The American Journal of CARDIOLOGY

AMERICAN COLLEGE OF CARDIOLOGY

OFFICIAL JOURNAL OF THE *American College of Cardiology*

Symposium on Ventricular Septal Defects

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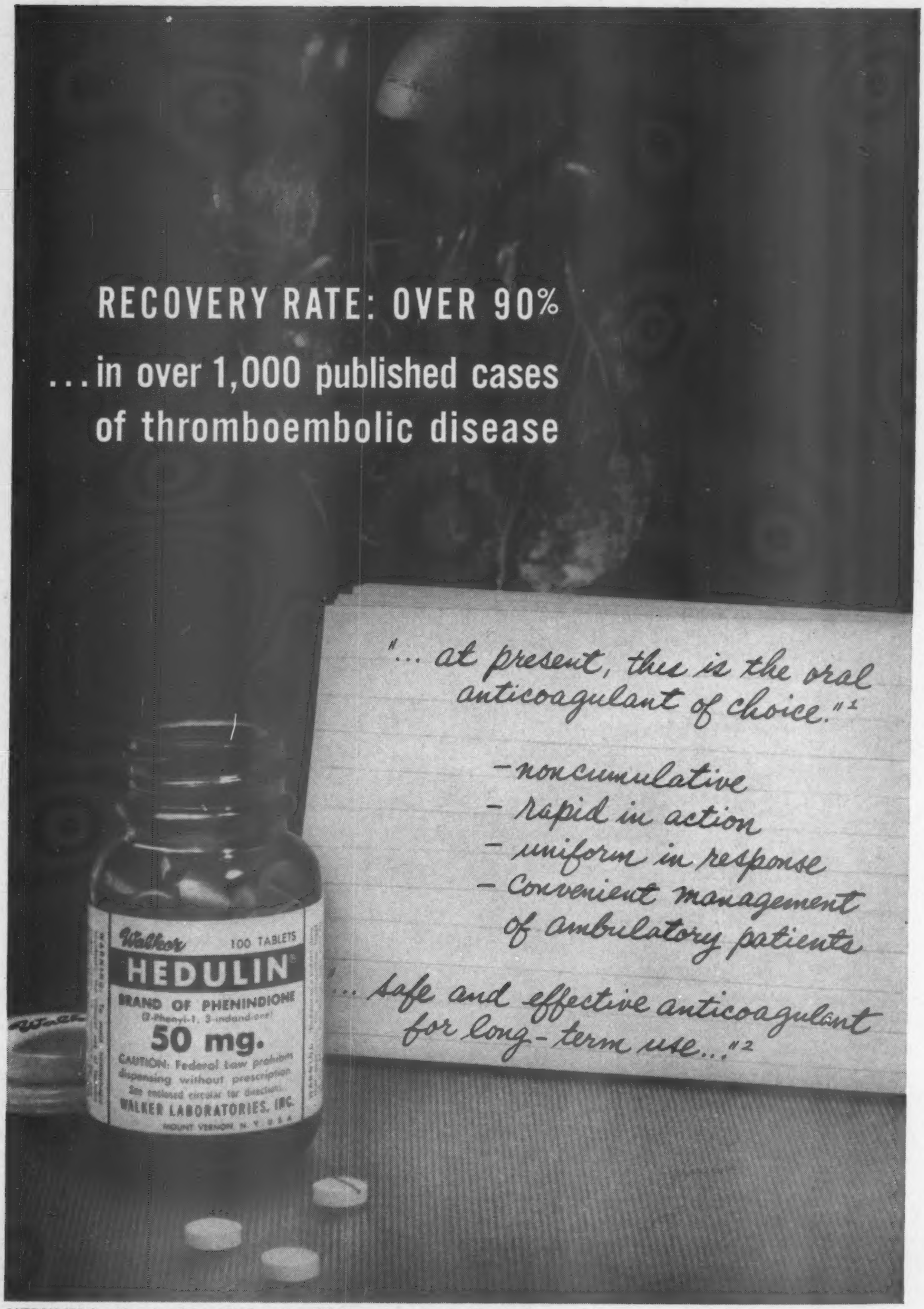

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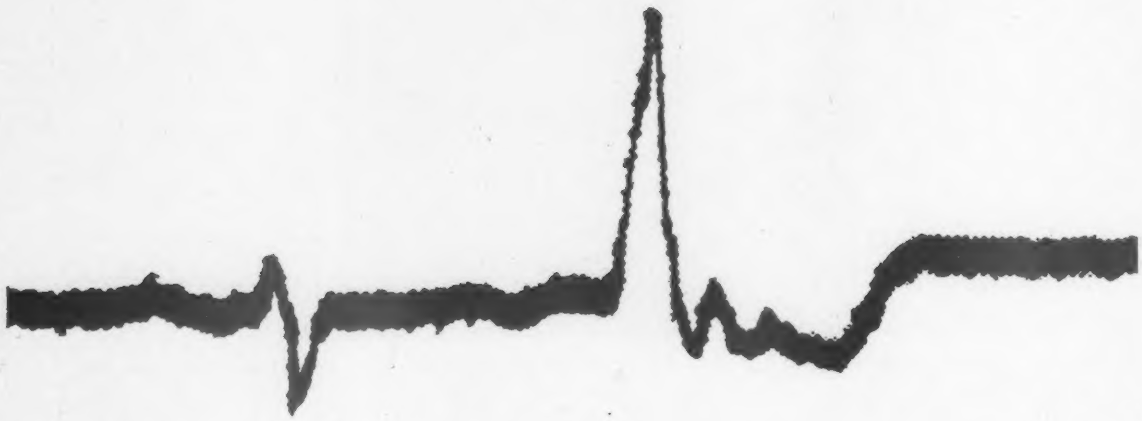

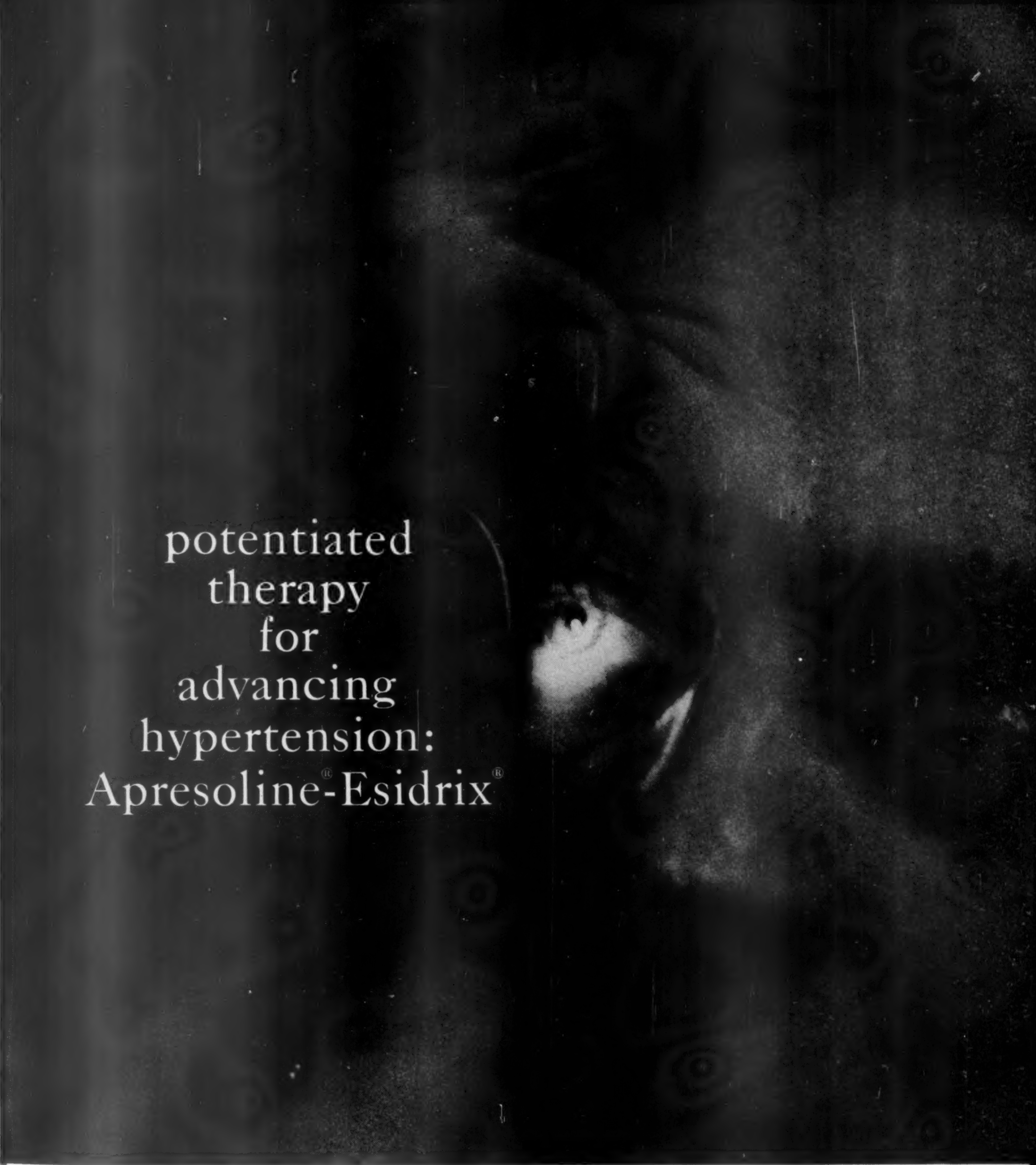
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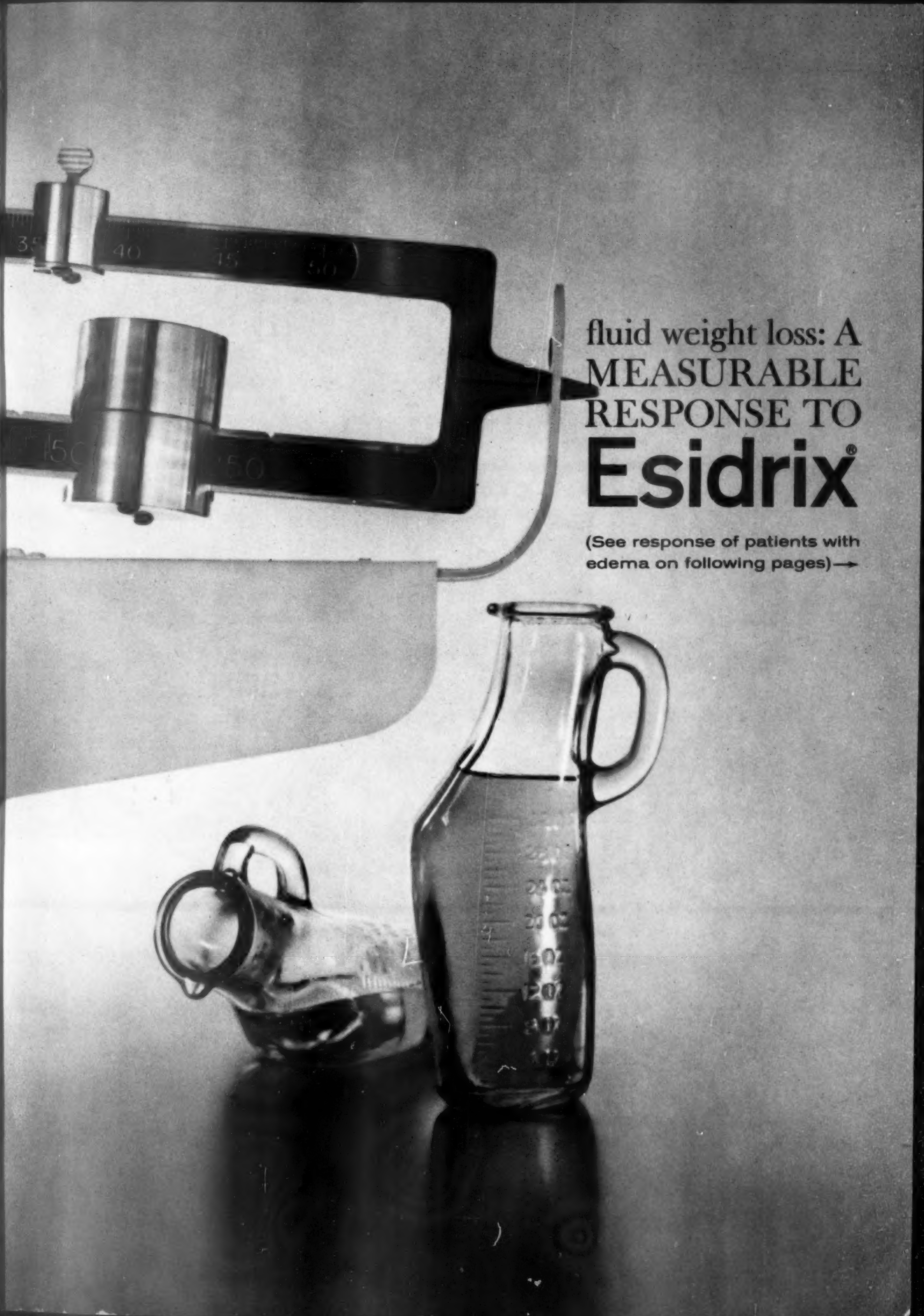
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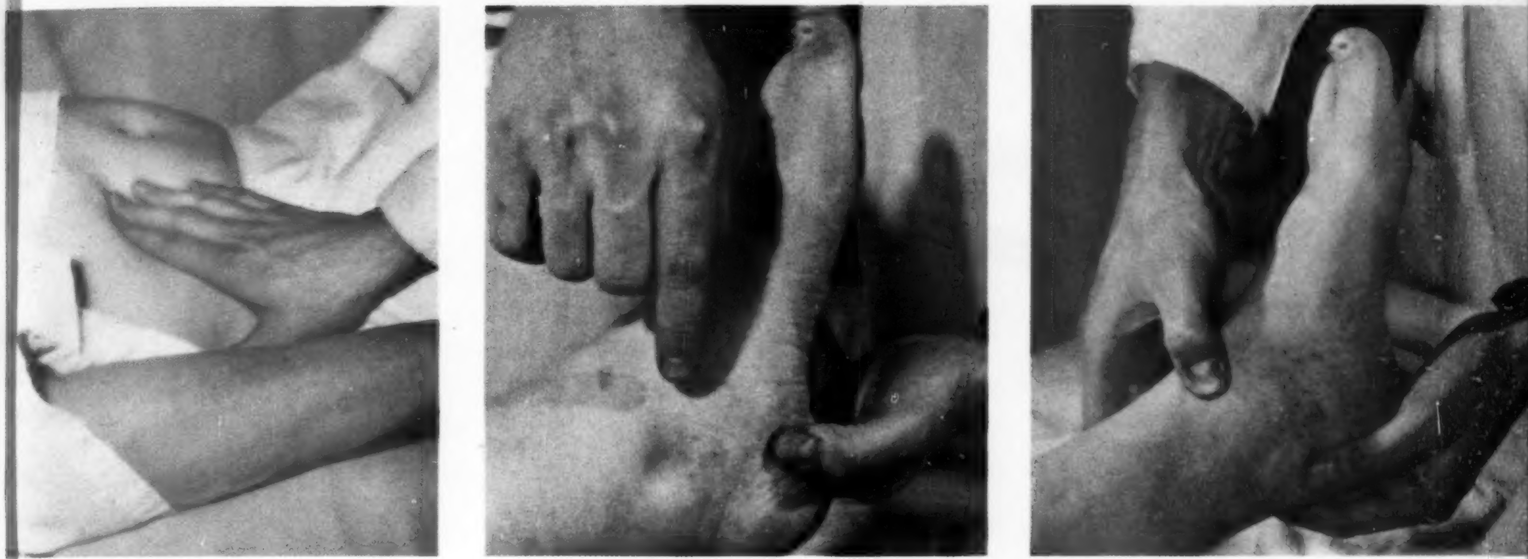

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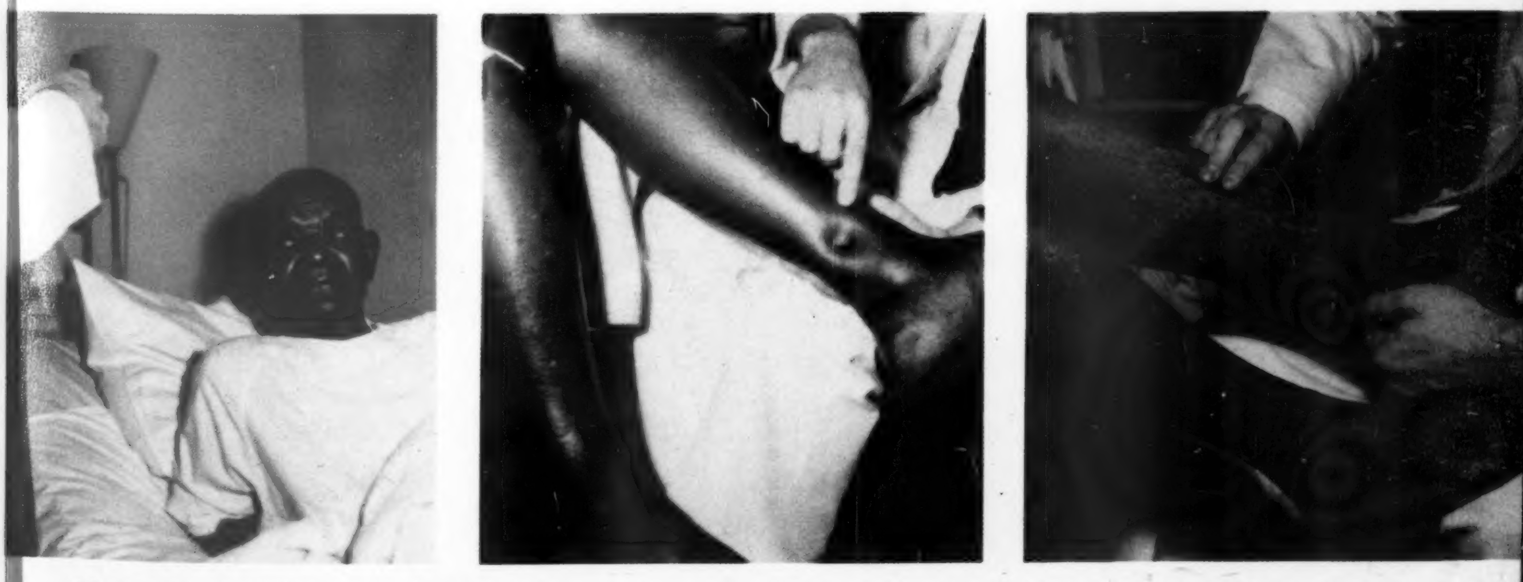

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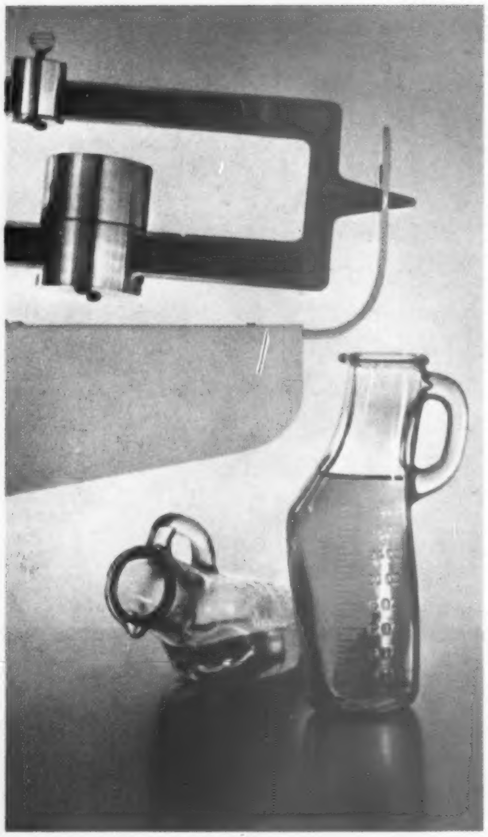

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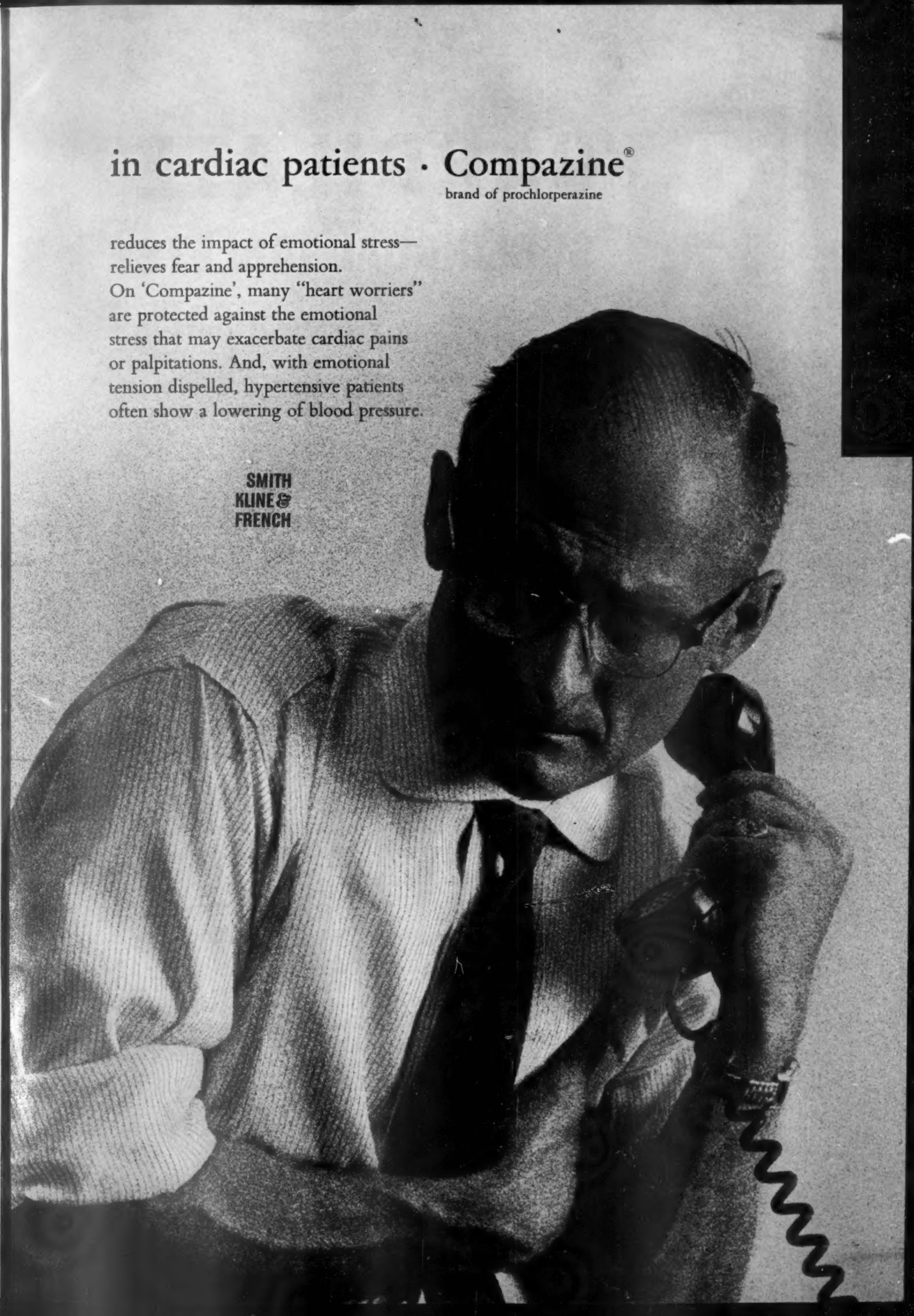
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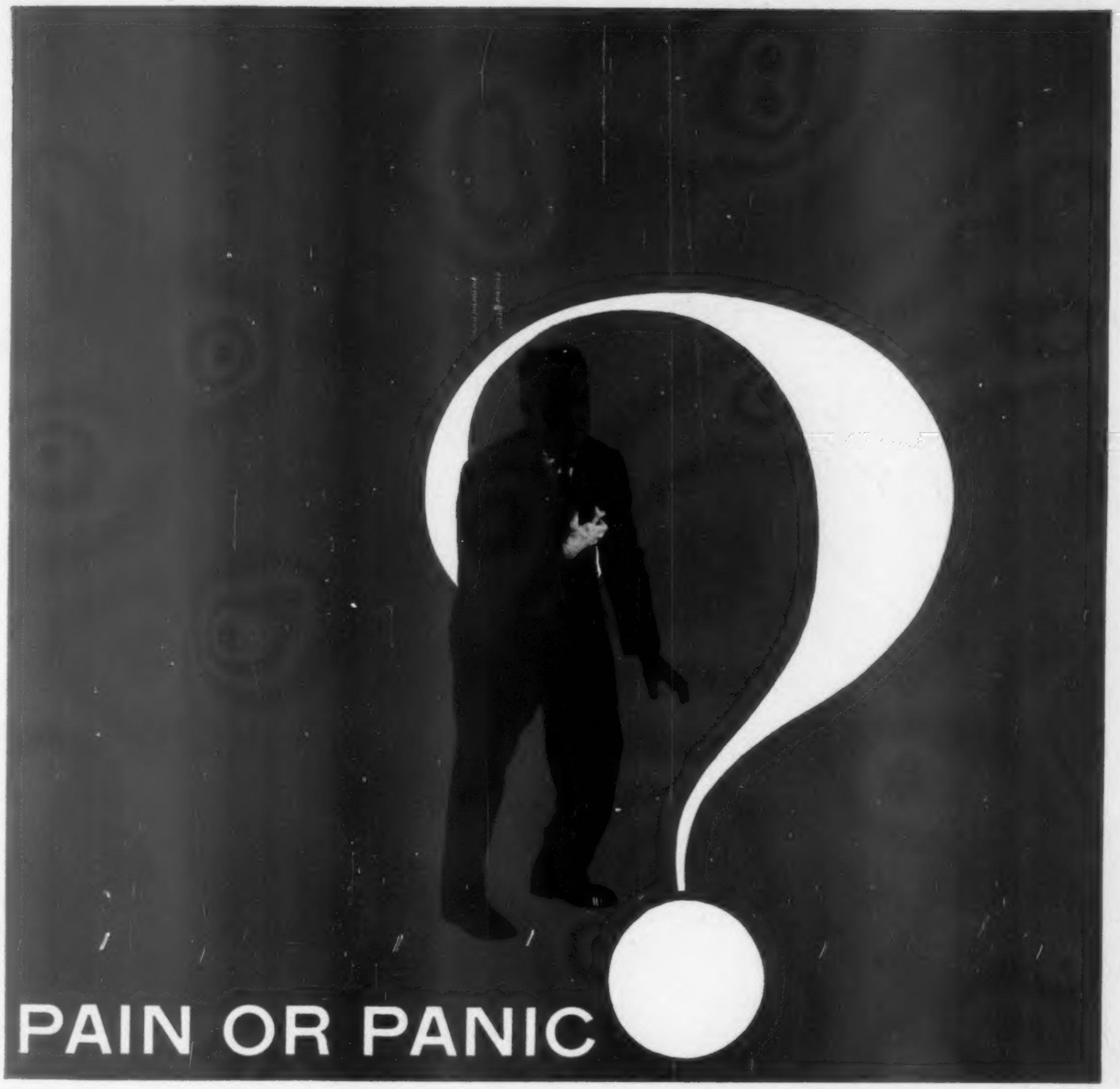
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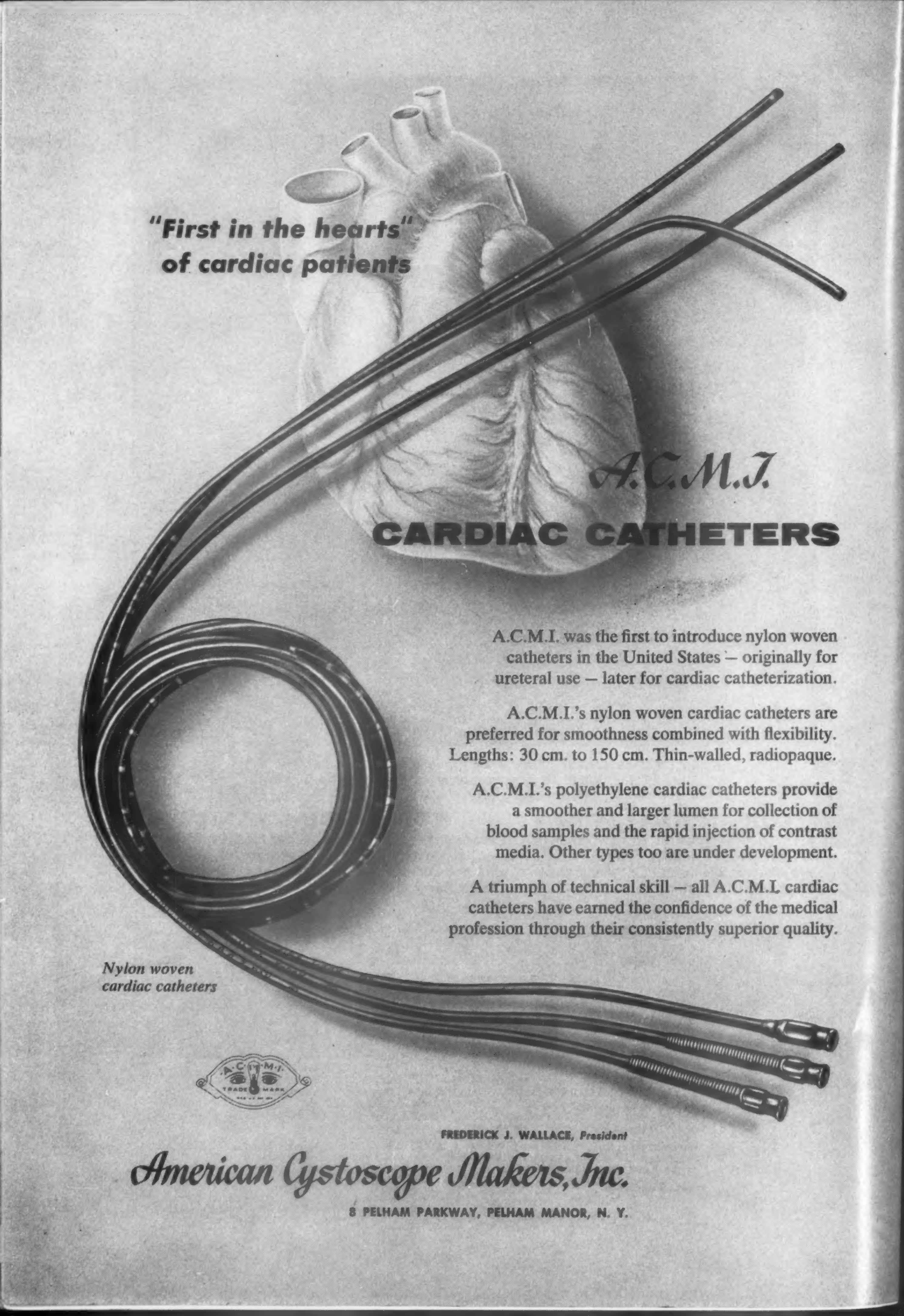
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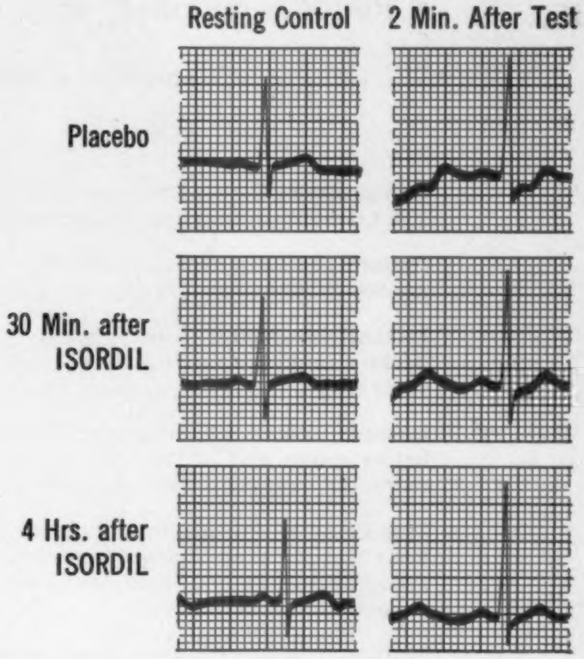

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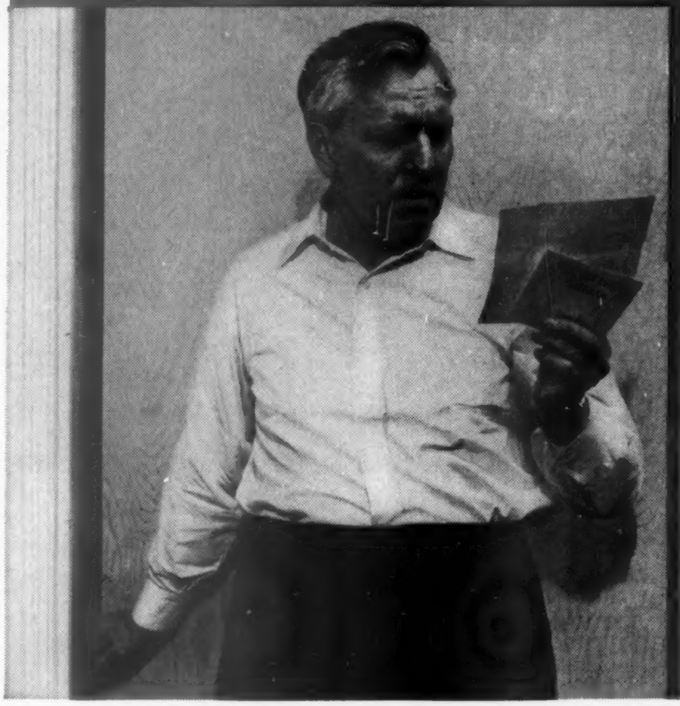

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Symposium on Ventricular Septal Defects

Introduction

TWENTY-FIVE years ago, surgery on the heart or great vessels was unheard of, except for a rare case or an experimental procedure in animals. Logically and factually, conquest of defects of extracardiac structures came first. Patent ductus arteriosus and coarctation of the aorta soon became correctible lesions. Fortunately, too, proper operative procedures under proper conditions resulted in actual cures.

Entry into the heart seemed and, in truth was, much more formidable. Only a dozen years have passed since surgical intervention for amelioration of valvular deficiencies became, or rather, started to become, a feasible procedure. Today, many different varieties of valvular deformity, either congenital or acquired, lend themselves, if not to complete restoration, at least to repair and functional improvement, and wondrous is it indeed, that these surgical miracles are accomplished daily, with risk of morbidity and mortality reduced to relatively insignificant levels. These levels, too, are being forced down constantly by improvement in the skill and experience of the surgeons and by refinements of technic.

Cardiac surgeons have not accepted these successes tacitly. They have pushed onward. They have insisted on continuing progress against any and all types of cardiac and vascular defects. Patent septa, incomplete closures, rotations and combinations of abnormalities are undertaken as problems for surgical correction. Technics for slowing cardiac activity and for reducing blood flow through the heart during surgery have been developed to the point where these fantastic, heroic operative procedures become mundane and prosaic. The cardiac surgeons continue to whittle away at the various types of defects, they develop new technics, they lower surgical risks.

In the ensuing Symposium on Ventricular Septal Defects, some of the current concepts, problems, approaches and hopes for the future are recounted. The future has no horizon. In these pages the readers will find factual information concerning this lesion derived from intensive clinical studies in the past decade, stimulated by the advent of open heart surgery. These include studies in the life history; physiologic disturbance; clinical diagnosis, including radiology, electrocardiography and phonocardiography; selection of patients for surgery; and the problem and results of repair of the septal defect.

More remarkable than all the surgical feats will be the future discovery of methods of preventing all these defects. Then the surgeons will seek new fields in which to pioneer.

MILTON S. SASLAW, M.D., F.A.C.C.
National Children's Cardiac Hospital
Miami, Florida

Anatomy, Physiology and Natural History of Simple Ventricular Septal Defects*

J. FRANCIS DAMMANN, JR., M.D., F.A.C.C., W. M. THOMPSON, JR., M.D.,† OMAR SOSA, M.D.‡ and IGNACIO CHRISTLIEB, M.D.§

Charlottesville, Virginia

THE truly remarkable progress toward the total correction of ventricular septal defects has made mandatory an increased understanding of such defects by specialists of many disciplines as well as the clinician and surgeon. This symposium on ventricular septal defects therefore certainly is timely. It will serve not only to collate the experience of many investigators, but also to point up those areas of understanding, as yet deficient, where additional clinical and animal research is sorely needed. In this portion of the symposium we shall deal with the structural anatomy of isolated ventricular septal defects and the known alterations in cardiopulmonary physiology which result. By the use of case material from our own files we shall attempt to set up diagnostic criteria for each of the many clinical syndromes which may be seen in patients with simple ventricular defects both to improve the selection of patients, and the timing of surgical correction.

ANATOMIC CONSIDERATIONS

DEFECTS OF MEMBRANOUS SEPTUM

The membranous portion of the ventricular septum is the last to complete its development. It is formed by the fusion of outgrowths of connective tissue arising inferiorly from the crest of the muscular septum, superiorly from ridges dividing the conus and truncus arteriosus, and laterally from the right atrioventricular canal cushions. Failure of any of these three outgrowths to develop normally leads to a membranous defect. Furthermore, if there is faulty timing in growth, fusion may not take place because one outgrowth may have lost its ability to fuse. Thus, it is not at all surprising that the membranous defects make up the vast majority of ventricular septal malformations.[1,2]

Location: The membranous septum on the left ventricular side lies in the outflow tract of the left ventricle immediately beneath the right coronary and non-coronary leaflets of the aortic valve. A membranous defect, consequently, is situated at the base of the aortic valve, separated from the leaflets only by a narrow band of connective tissue and, at times, by no tissue at all. At its inferior margin the membranous septum fuses with the right ventricular side of the muscular septum. The relationship of the origin of the aorta to the membranous septum is somewhat variable, but usually is such that when a membranous septal defect is present the aorta appears to override the septum. The degree of overriding depends upon the magnitude of rotation of the aorta and pulmonary artery and also on the extent that the ventricular septum bulges into the right ventricular cavity (Fig. 1). Furthermore, the plane in which the muscular septum and aorta lie is such that any straightening out of the aorta directs the aortic valve even more strikingly toward the right ventricular chamber. Thus, some overriding is the rule when a membranous septal defect is present.

On the right ventricular side the membranous septum lies behind the septal, or the septal and anterior leaflets of the tricuspid valve. Commonly, tricuspid chordae tendineae may insert into the fibrous margin of the defect. In contrast to the aortic valve, which forms the superior margin of the membranous septum on the

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‡ Teaching Fellow, National Heart Institute, National Institutes of Health, U. S. Public Health Service.

§ Organization of American States, Fellow in Cardiovascular Surgery.

left, the tricuspid valve arises from the mid-portion of the membranous septum (Fig. 2), and consequently the upper portion of the membranous septum on the right forms part of the right atrial wall. Because of this relationship, a membranous septal defect may exist in which the defect brings left ventricle and right atrium into direct communication.[3]

The outflow tract of the right ventricle is bounded above by the pulmonary valve, and below by the heavy muscular mass of crista supraventricularis. It lies medially and superiorly to the origin of the septal leaflet of the tricuspid valve. Under the prolonged stress of a high pulmonary blood flow and high pulmonary pressure, hypertrophy of the right ventricular outflow tract may occur, leading to a relative infundibular stenosis and a distinct pressure differential between the right ventricular chamber and the pulmonary artery.

A-V Conduction Pathways: The major conduction pathways from the atrioventricular node to the right and left ventricles are intimately related to the membranous septum.[4] The atrioventricular node is located on the atrial side of the fibrous ring, close to the base of the medial tricuspid leaflet, medial to the limbus fossa ovalis and superior to the ostium of the coronary sinus. The node gives origin to the atrioventricular bundle of His which courses to the left toward the apex, penetrates the fibrous ring and reaches the membranous portion of the ventricular septum posterior and inferior to the common site of a defect (Fig. 3). In its subendocardial position, it passes anteriorly following the posteroinferior rim of the defect. As it progresses ventrally, it branches into a right bundle which courses down the right ventricular septum toward the main right papillary muscle, and a left bundle which is less distinct and gives off numerous small fasciculi[5,6] rather than continuing as a single unit.

It is important to know the position of the conduction system when correcting membranous defects surgically so as to avoid the not infrequent and serious complication of complete heart block which so often terminates fatally. In most cases the conduction system lies so close to the endocardium and to the posteroinferior margin of the defect that sutures in this area cannot be placed superficially enough to exclude the conduction fibers. Considering the fact that the bundle approaches the membranous septal defect from the right side and that, after division, the right branch continues down

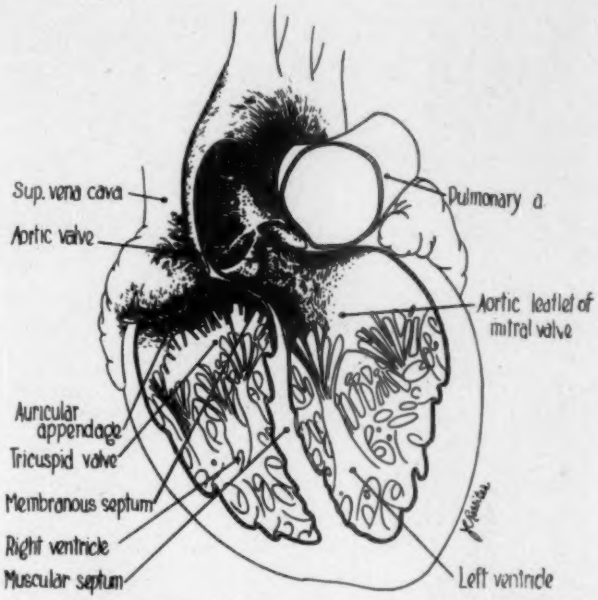


FIG. 1. Diagram of the muscular and membranous septum in relation to the origin of the aorta. Note that in the absence of the membranous septum the aorta would appear to override both ventricles.

as a unit, whereas the left divides in multiple fasciculi, the area to which the surgeon should pay the most attention seems to be the right

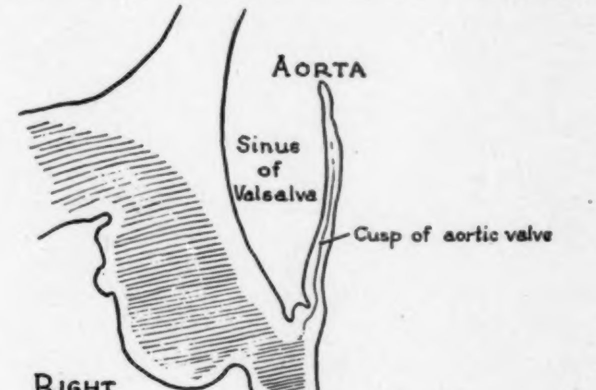


FIG. 2. Diagram of the relationship of the membranous septum to the left ventricle, right ventricle and right atrium. (From: FERENCZ, C. *Bull. Johns Hopkins Hosp.*, 100: 209, 1957.[3])

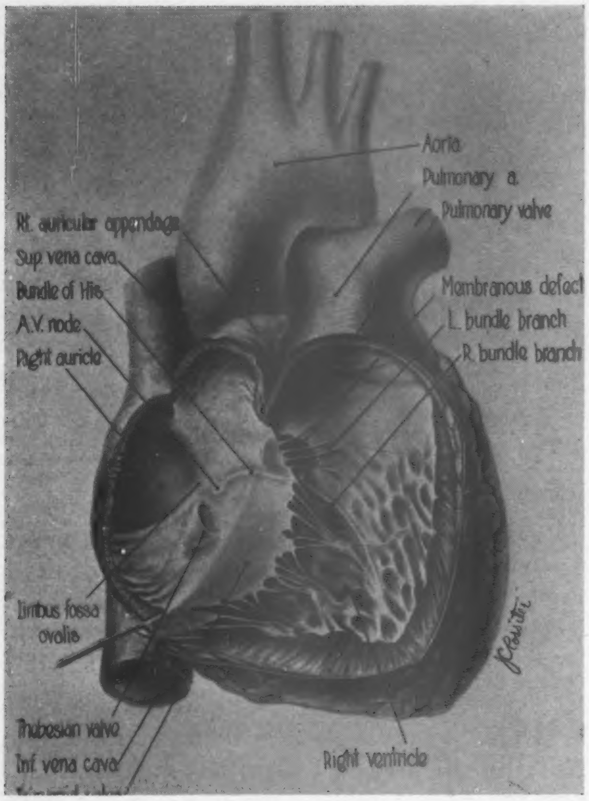


FIG. 3. Composite drawing of the right atrium and ventricle to demonstrate the relationship of the conduction system to a membranous septal defect.

posteroinferior "corner" of the defect. Repair of membranous defects under direct vision, without stopping the heart's function by artificial arrest, and with continuous observation of the electrocardiogram, has proved, in our hands, the best means of avoiding significant damage to the conduction system of the heart. Also, every attempt to avoid potentially harmful complications which may increase the likelihood of complete heart block must be made. Such complications include myocardial anoxia, acute ventricular and atrial dilatation, and the use of agents to produce ventricular standstill, which may be toxic to the conduction system.

DEFECTS OF MUSCULAR SEPTUM

A second type of ventricular septal defect lies in the muscular septum. Such defects are far less common than membranous defects, but are most likely to be multiple. During the early stages of cardiac development, the muscular ventricular septum first appears as a trabeculated ridge which, as it grows, tends to become more and more of a muscle mass in which the intertrabecular spaces become smaller and finally disappear. If an intertrabecular space fails to seal, a communication between the right and left ventricle will remain. Edwards[7] has made the observation that such defects in infancy appear as ovoid in shape, whereas in the adult they tend to lengthen out so that the edges almost meet. The physiologic importance of this observation will be discussed later. Muscular defects have the advantage of not being located close to the conduction system and, hence, complete heart block during surgical closure is less common.

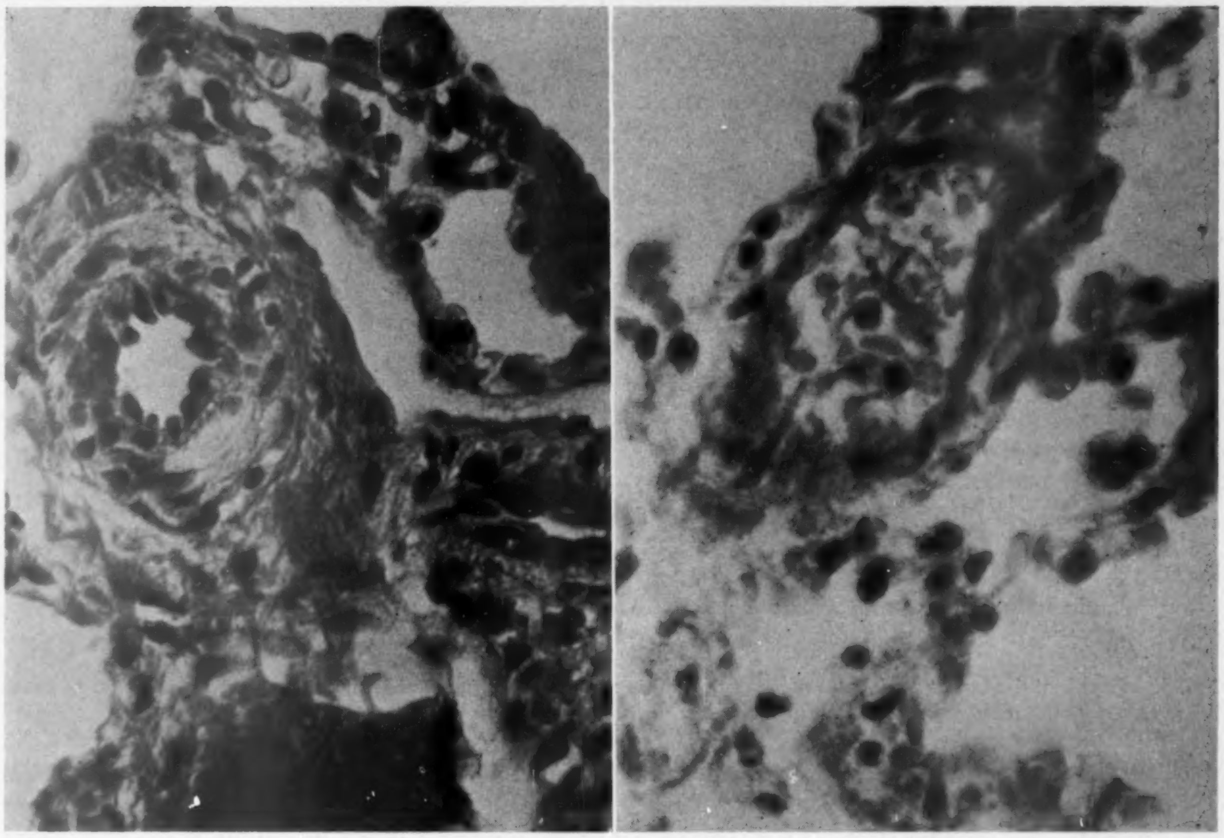
PHYSIOLOGIC CONSIDERATIONS

CHANGES IN PULMONARY CIRCULATION FOLLOWING BIRTH

Knowledge of the normal fetal and neonatal relationship between the systemic and pulmonary circulations is of paramount importance in understanding the role that a ventricular defect may play in altering hemodynamics. In essence, a ventricular septal defect prolongs the intimate fetal relationship between the systemic and pulmonary circulations into postnatal life. The normal evolutionary pattern followed by the pulmonary vascular bed is interfered with and this accounts in part for the clinical course seen in patients with ventricular septal defects. A review of the fetal and neonatal circulations therefore, should constitute the natural beginning for any discussion of the physiology of ventricular septal defects.

Fetal Circulation: The fetal circulation is essentially a single circulation, in which the pulmonary vasculature exists in parallel and not in series with the systemic circulation, just as does the circulation of the liver, kidney and brain. Blood may bypass the lungs both proximal and distal to the heart. Inferior vena caval blood is deflected into the left atrium by the valve of the foramen ovale. Blood that reaches the right ventricle for the most part bypasses the lungs through the patent ductus arteriosus into the descending aorta. Consequently, changes in pulmonary vascular resistance merely increase or decrease the proportion of blood diverted to the lungs and, except under unusual circumstances, do not materially affect blood flow to the rest of the body. Bypass of the lungs is brought about by the existence of a pulmonary vascular resistance that is at least equal to that in the systemic circulation.

In fetal life, pulmonary vessels are surrounded by a fluid media, are relatively thick-walled, and small-lumened, and compare closely to com-



A B

FIG. 4. Photomicrographs of small muscular pulmonary arteries. A, obtained from a newborn infant. B, obtained from a four month old infant. Note the remarkable relative and absolute increase in lumen size and decrease in wall thickness.

parable vessels in the systemic circulation. Fetal hemodynamics are in no way altered by the addition of a ventricular septal defect since the defect serves simply as another route by which the lungs may be bypassed. Ventricular output, ventricular capacity and peripheral vascular resistance are not materially affected.

Neonatal Circulation: Normally, the fundamental change which occurs as a consequence of birth is the division of this single circulation into two separate and yet interdependent circulations. The infant's first breath produces a remarkable decrease in pulmonary vascular resistance. Fetal pulmonary vessels, heretofore supported by fluid media, are suddenly suspended in air. New vessels are opened and already patent vessels enlarge. Pulmonary arterial pressure falls, pulmonary blood flow increases manyfold, and pulmonary vascular resistance decreases to such an extent that within a few days two- to threefold increase of pulmonary blood flow is not accompanied by a significant rise in pulmonary arterial pressure.[8,9] Increased pulmonary blood flow increases return to the left atrium, increases left atrial pressure and produces closure of the foramen ovale. The sudden increase in arterial blood oxygen tension, which follows the shift in oxygen dependence from the placenta to the fetal lungs, produces a constriction of the ductus arteriosus, which is followed within a few days by total anatomic closure.[10]

The closure of the foramen ovale and the ductus arteriosus serves to alter the circulation from several parallel circulations to one which is serial. In contrast to the fetus, alterations in the systemic circulation directly affect pulmonary blood flow and, conversely, shifts in the pulmonary circulation directly affect systemic blood flow. The lung is no longer an independent organ which can draw on a bank of circulating blood as can the liver, spleen and gastrointestinal tract. The lungs become a low pressure system which must accept all blood returning from the systemic circulation, oxygenate and remove carbon dioxide and return that blood to the systemic arterial bed. The structural vascular change which follows this

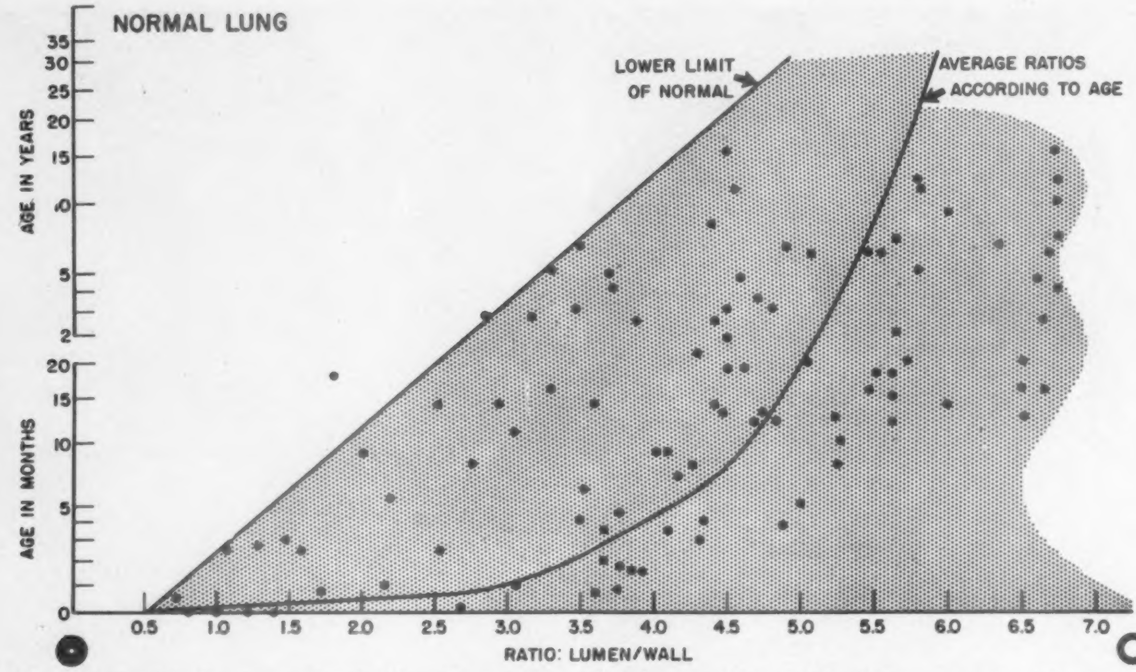


Fig. 5. Graph of the lumen:wall ratio of small muscular pulmonary arteries obtained from normal patients of varying ages. Note the relative increase in lumen size and decrease in wall thickness occurring with age.

marked fall in pulmonary blood pressure, resistance and vasomotor tone consists of gradual enlargement; the muscular media of the pulmonary vessels becomes thin, the lumen is greatly increased (Fig. 4). Within the period of a few months there is a remarkable shift in ratio of pulmonary vessel wall thickness and lumen size (Fig. 5).

Changes in Pulmonary Vessels Following Birth: Burton's classic analysis[12] of the function of blood vessels in terms of recognized physical laws affords an explanation for the change that occurs in pulmonary vessels following birth, as well as their increased susceptibility to injury after birth. The size of a vessel with a certain distensibility and vasomotor tone is determined by its transmural pressure. The transmural pressure may be defined as the difference between intravascular (blood) pressure and the surrounding tissue pressure. Following birth the pulmonary vessels become surrounded by air, not fluid, thus reducing extravascular pressure. Furthermore, expansion of the chest cage and the periodic negative intrathoracic pressure developed during the respiratory cycle decrease the external pressure exerted on the vessel walls even more. Effective transmural pressure is increased. The result is dilatation of vessels already patent, and the opening of vessels heretofore closed. This remarkable increase in lumen size effectively decreases pulmonary resistance so that less driving pressure is needed to force the total right ventricular output through the pulmonary circulation. The pressure drop across the pulmonary vascular bed is decreased. Vasomotor tone decreases, since distending pressure is less, and disuse atrophy of the vessel media occurs. Resistance to driving pressure is also definitely decreased by the straightening out of vessels from the mechanically kinked state found in the partially collapsed lung.[13,14] The result of these changes is a shift from a high pressure, high resistance vascular bed with a relatively small cross-sectional area and high vasoconstrictive tone to a low pressure, low resistance bed with a large cross-sectional area.

EFFECT OF INCREASED STRESS ON CIRCULATION

Changes in Pulmonary Vessels: Such a vascular bed is well adapted to normal pulmonary circulation. However, it is most susceptible to injury resulting from stress. According to the law of Laplace, the tension required in the vessel wall to resist dilatation is a function of pressure in the vessel multiplied by the radius of the vessel.[15] Increases in blood pressure, which may be brought about by increasing flow significantly, by decreasing functioning lung tissue to a minimum or by increasing left atrial and pulmonary venous pressure, exert far more tension on the large lumined pulmonary vessels than a

similar pressure increase would exert on systemic vessels. Furthermore, both the muscle mass, which controls active vascular tension, and the extravascular pressure are much less than in either fetal pulmonary vessels or normal systemic vessels. One might anticipate therefore, that increases in pressure in the adult pulmonary vessel would result in dilatation of this vessel. Such, indeed, is the case. Only when the vessel is stretched to the limit of its surrounding fibrous jacket, does the flow pressure curve become linear. At this point, each added increment of flow is accompanied by an added increment of pressure and vessels stretched to their limit probably are injured. Severe and acute injury leads to a break in the vessel wall, the loss of blood constituents into the various layers of the vessel wall and an acute inflammatory arteritis. Less severe and more chronic injury leads to a proliferation of the protective fibrous coat, an increase in medial muscle mass and intimal injury changes characterized by cellular and hyaline proliferation.[16–18]

With this analysis in mind, it becomes clear why the degree of pulmonary injury associated with congenital heart disease depends not only upon the size of the defect, but also upon the point in development of the patient at which the lungs are stressed. The pulmonary vascular bed is better able to withstand stress, for vessel diameter is less and medial thickness is greater. The likely response of such vessels is increased thickening of both media and adventitia, with intimal injury occurring later. Stress, reaching significant levels after several months of extrauterine life have passed, finds a vascular bed much more susceptible to injury.[19]

Effect of Increased Workload on the Ventricles: The pulmonary vascular bed, its relationship to the systemic circulation, and the degree to which it is altered by the presence of a ventricular defect, constitute one of the areas which must be understood completely in order to comprehend the natural history of cardiac malformations. A second area is the analysis of the degree and form of stress placed on the right and left sides of the heart. Fundamentally, the work load of either the right or left ventricle can be altered in one of two ways.

(1) Change in peripheral resistance against which the ventricle must work is the first. An increase in peripheral resistance increases the driving force necessary to propel blood through the peripheral circulation. This demands an increase in ventricular and muscle mass force. In the absence of congestive heart failure ventricular hypertrophy *per se* usually is not manifested by a change in heart size. However, the contour of the heart does change. For example, left ventricular hypertrophy produces a rounding of the apex of the heart (concentric hypertrophy) as viewed in the posteroanterior or left anterior oblique position. Systolic or pressure overload of the left ventricle inscribes a pattern in the electrocardiogram characterized by a swing of the mean spatial vector to the left and posteriorly, an increase in the amplitude of the right precordial S waves and left precordial R waves and by inversion and depression of the left precordial T waves. Pressure overload of the right ventricle is characterized by a swing of the mean spatial vector to the right and anteriorly, an increased amplitude of the right precordial R wave frequently associated with inversion and depression of the right chest T waves.

(2) The second factor altering work load is volume load. In the presence of a constant pulse rate, an increased cardiac output can only be produced by increasing the stroke volume. Changes in stroke volume obviously alter total cardiac size. Increased stroke volume of the left ventricle displaces the apex of the heart laterally and inferiorly so that the heart assumes a 45 degree angle. Increases in right ventricular stroke volume cause anterior enlargement of the right ventricle which, in childhood, produces a precordial bulge. The electrocardiographic expression of an increased volume load of the right ventricle is the appearance in the right chest leads of an RSR′ pattern and a widening of the QRS complex primarily over the right chest leads. Increased left ventricular volume load is characterized by large late R waves in the left chest leads and strongly upright T waves with a coved ST segment.

EFFECT OF SEPTAL DEFECTS ON THE VENTRICLES

Left Ventricle: In patients with ventricular septal defects an understanding of the degree and type of workload increase of the two ventricles is obviously important in evaluating the form of defect with which the clinician is dealing. When the left-to-right shunt is large, the return of blood to the left side of the heart will be increased and yet the resistance against which the left ventricle must work is not increased. Thus, the left ventricle reflects increased volume load both by x-ray and electrocardiogram. When the shunt is absent, since there is no increase in volume to be handled by the left ventricle and

systemic resistance is normal, the left ventricle is normal. When a right-to-left shunt exists through a ventricular septal defect, return of blood to the left ventricle is normal or reduced, systemic resistance is normal and the blood ejected from the right ventricle escapes directly through the aortic valve lying directly above the membranous septal defect without influencing the left ventricle.

Right Ventricle: When pulmonary resistance and pressure are low, there is no increase in pressure workload of the right ventricle and consequently no evidence of electrocardiographic systolic overloading of the right ventricle. If the shunt from left to right is significant it does produce a volume overload of the right ventricle because the membranous defect lies behind the tricuspid valve and proximal to the outflow tract of the right ventricle; consequently shunted blood must pass through the right ventricle. The right ventricle appears enlarged both by physical and fluoroscopic examination and by the presence of an RSR′ pattern in the right precordial leads. When the shunt is small and right ventricular pressure is normal, there is no right-sided enlargement. When the shunt is small and the pulmonary artery or right ventricular pressure is raised, the right ventricle is hypertrophied and there is a systolic or pressure overload pattern in the electrocardiogram. The combination of high flow and moderate elevation of right ventricular pressure produces a large right ventricle and a pattern of rSR′ often associated with T wave changes in the right chest leads plus a deep and wide S in the left precordial leads.

Thus the relative size of the two ventricles, their contour and the electrocardiographic pattern serve as indicators as to the nature and degree of stress caused by a ventricular defect. Serial studies bring to light changes in stress which are even more informative.

We have shown that during fetal life the presence of a ventricular septal defect in no way alters hemodynamics and places no unusual stress on the lungs. However, after birth, the normal adaptation to extrauterine life is surely altered. The magnitude of shunt related to the functional size and position of the defect as well as the response of the pulmonary vasculature are primary factors which determine the clinical course. Of secondary importance, is the ability of the left ventricle to handle the added load, for left ventricular failure or a rise in left ventricular pressure will further burden the pulmonary circulation.

Large Ventricular Defect

We may define a large ventricular defect as one which does not limit the volume of shunt or offer a resistance to passage of blood through the defect. The quantity of blood flow through the pulmonary and systemic circulations is regulated solely by the peripheral resistance of each circulation. Systolic pressure in the right and left ventricles is the same and a common ejectile force exists. Mean pressures are not the same since the diastolic pressure in each circulation is dependent on the vascular resistance. Following birth not only does pulmonary vascular resistance fall, but the removal of the low resistance placental vascular bed from the systemic circulation by clamping the umbilical cord, also raises systemic resistance and pressure. It is small wonder that stress on the lungs is frequently excessive. There is either progressive vascular dilatation or an acute injury response. Dilatation which decreases pulmonary vascular resistance diverts an ever-increasing percentage of the total cardiac output through the defect to the lungs. High output failure and death may result.

In some patients, however, the response is different. Dilatation and stretch of vessel wall is accompanied by high vasoconstrictive tone and is followed by gradual hypertrophy of the media and usually by intimal sclerotic changes as well. This effectively increases pulmonary vascular resistance, leading to an increase in mean pulmonary artery pressure and a decrease in pulmonary blood flow. Signs of cardiac failure abate. Growth and development become essentially normal. Exercise tolerance improves. The course of the patient suggests that the defect is closing. Anatomically, such is not the case, but from the physiologic standpoint, the defect has become less significant. Eventually, pulmonary vascular resistance may exceed systemic vascular resistance. Pulmonary mean pressure, therefore, is high and the direction of blood flow through the ventricular defect is from right to left and not left to right.[20]

The size of the defect was related to hemodynamic alterations in forty patients with ventricular septal defect in whom analysis was made both by cardiac catheterization and by observation at the time of surgery by Wood and his associates.[21] Defects larger than 1 cm. per M^2 of body surface may be said to result in essen-

tially a common ejectile force in the ventricles and to represent large defects. When the diameter of the ventricular defect is less than 1 cm. per M^2 of body surface the ventricles do not have a common ejectile force and the patients may be said to have a medium or small-sized defect.

ILLUSTRATIVE CASES

The progression of signs and symptoms in patients with a large defect of the membranous septum may be illustrated by two case histories.

CASE 1. *Progression From High Output Failure to Phase of Balanced Flows and Pulmonary Hypertension:* J. W. S. was a four and a half year old boy who, during the first three months of life, was admitted to a hospital on three separate occasions because of feeding difficulty, vomiting, failure to gain weight, rapid respirations and hoarseness. Just prior to the third hospital admission a harsh, low pitched, systolic murmur, unassociated with a thrill was noted. The pulmonary second sound was loud but not reduplicated. The liver and spleen were enlarged. A partial paralysis of the left vocal cord was observed on direct laryngoscopy. X-ray examination revealed marked cardiac enlargement chiefly involving the left ventricle and atrium, a convex main pulmonary artery segment and hypervascular lung fields. The tentative diagnosis was endocardial fibroelastosis. During the next two years, weight gain improved, the incidence of pulmonary infections decreased, and dyspnea with exercise and feeding abated.

Clinical and Catheterization Findings: The patient was readmitted to a hospital at the age of three with a diagnosis of possible atrial septal defect. There was a left precordial bulge, a moderately loud, systolic murmur maximal in the second left interspace and a loud pulmonary second sound. An occasional wheeze was heard over the lungs posteriorly. The tip of the liver was palpable and slightly firm. X-ray examination revealed slight cardiac enlargement, a prominent main pulmonary artery and increased pulmonary vascular markings. Cardiac catheterization (Table I) suggested the diagnosis of a ventricular septal defect with pulmonary hypertension, a left-to-right shunt at rest and minimal right-to-left shunt with exercise.

Subsequent Course and Operative Findings: Between the ages of three and four and a half the patient gradually improved, showing less ease of fatigue, greater tolerance for exercise, less susceptibility to infection and an improved appetite. At age four, there was a distinct bulge to the left side of the chest. The heart did not appear to be enlarged and precordial activity was not increased. There was a short, rough, moderately loud systolic murmur which could be heard all over the precordium, but was maximal in the third left interspace. The pulmonary second sound was very loud and split. There was no evidence of congestive failure. On fluoroscopy, the lung fields appeared vascular and were actively pulsatile. There was a full main pulmonary artery, full right ventricular outflow tract and suggestive evidence of left atrial enlargement.

TABLE I

Case 1. Large Ventricular Septal Defect. Data Obtained from Cardiac Catheterization and During Surgery

Location	3 Years of Age		4 1/2 Years of Age		
			Preoperative		Postoperative Pressures (mm. Hg)
	Oxygen Saturation (%)	Pressures (mm. Hg)	Oxygen Saturation (%)	Pressures (mm. Hg)	
Cava	66	...	...	...	...
Right atrium	64	...	61	...	...
Right ventricle	81	112/0	...	...	...
Pulmonary artery	...	...	83	95/?	85/?
Femoral artery	93	105/88	100	95/?	115/?

A diagnosis of a large ventricular septal defect with pulmonary hypertension was made and the patient was referred to a center[22] employing extracorporeal circulation for closure of his defect. A large, high defect in the membranous septum was found at operation. Pressures and oxygen saturations are listed in Table I. Following closure of the defect, pulmonary artery systolic pressure fell to 85 and aortic pressure rose to 115 mm. Hg. On the morning of the fifth postoperative day he appeared restless and then suddenly stopped breathing. A continuous electrocardiographic monitor indicated that his heart slowed only after respirations had ceased. He could not be resuscitated.

At autopsy, examination revealed that the defect had been completely closed; the heart was slightly enlarged, right and left ventricular walls were equally thick. The small pulmonary arteries showed evidence of significant medial hypertrophy and intimal proliferation (Fig. 6). A few vessels were totally occluded. There was no hemorrhage, edema, congestion or evidence of recent thrombosis.

Comment: This patient illustrates the progression from the phase of high output cardiac failure, pulmonary congestion, failure to gain weight and a huge heart, to the phase of essentially balanced flows, improvement in exercise tolerance, growth and development and a smaller heart.

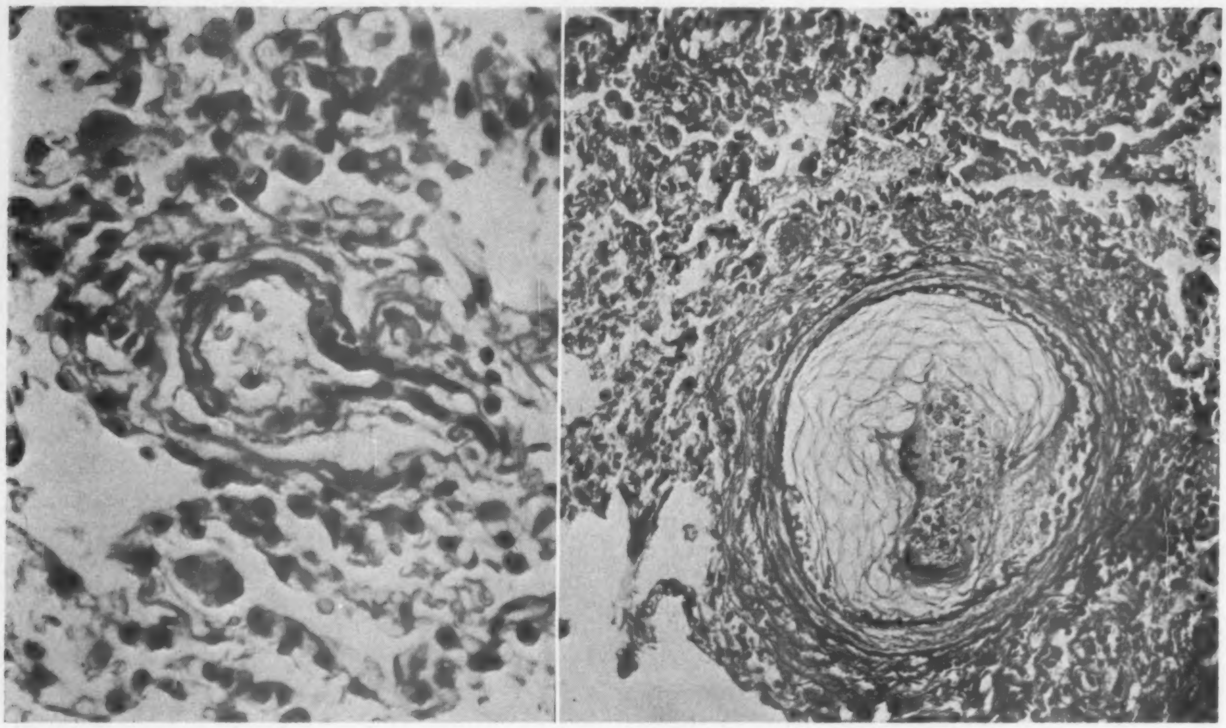


Fig. 6. Case 1. A, a terminal muscular artery and arteriole. Note the medial hypertrophy. B, a larger pulmonary vessel. Note the medial hypertrophy and almost complete obliteration of the lumen. Original magnification × 585.

Serial electrocardiograms accurately portrayed the clinical course (Figs. 7A and 7B). In actuality a single electrocardiogram considered with the clinical findings led to the erroneous diagnosis of endocardial fibroelastosis and atrial septal defect which would have been ruled out quite effectively had serial electrocardiograms been available. Furthermore, the progressive electrocardiographic changes, when considered together, should have alerted us to the rapidly progressive pulmonary vascular changes which caused the fatal outcome after surgical intervention.

Serial tracings revealed a shift from predominant left ventricular activity and strain to right ventricular preponderance. The most striking change occurred between the ages of three and eighteen months during the period when the patient's clinical condition was steadily improving. The nature of the change indicates that the patient's left-to-right shunt rather rapidly decreased due to a rising pulmonary vascular resistance. The rapidity of change and the early age at which it occurred suggest that the child may have been inoperable at the age of eighteen months. The appearance of such a progression in another patient would force us to consider early closure of the defect or protection of the lungs by the creation of pulmonary stenosis.

The form of death that occurred on the fifth postoperative day is that associated with pulmonary hypertension, despite the fact that pulmonary artery pressure dropped after closure, indicating that the basic shunt had been left to right.

Not all patients with large ventricular septal defects pass through the phase of frank high output cardiac failure. In some patients, a higher pulmonary vasoconstrictive tone is maintained after birth, and pulmonary flow does not reach excessively high levels. The predominant cardiac findings implicate the right ventricle starting in early infancy. The clinical course is less severe in the first year of life, but eventually excessive pulmonary hypertension with reversal of flow is more likely to occur.

Case 2. *Early Pulmonary Hypertension Without High Output Failure:* This five year old girl (P. L. R.) weighed 5 pounds and 12 ounces at birth and 33 pounds at the time of surgery. For the first four months of her life she was thought to be normal. A murmur was first heard during a routine examination at the age of four months. She had pneumonia at six months of age. Her appetite was always poor and weight gain slow. She was never noted to be cyanotic. She did

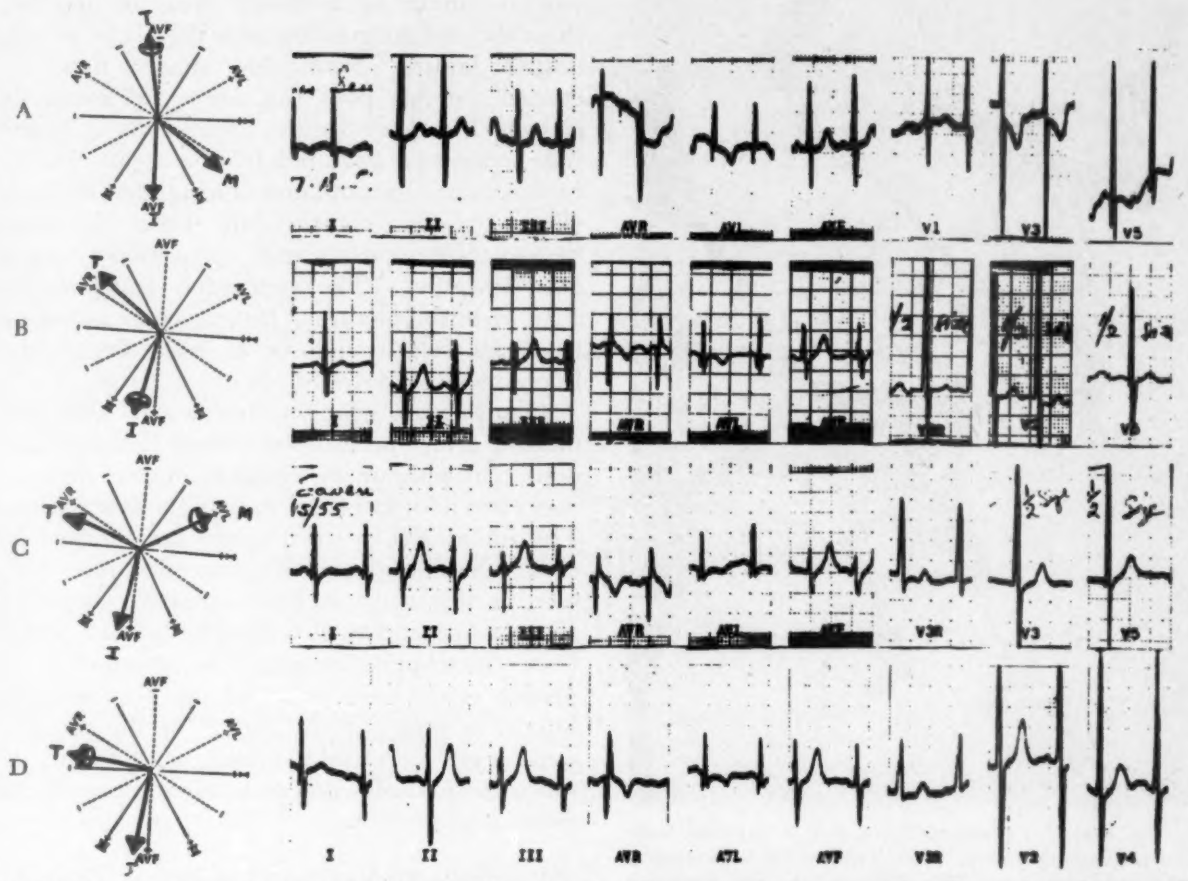


FIG. 7. Case 1. A, age three months. B, age fifteen months. C, age twenty-seven months. D, age forty-four months. *Left*, electrocardiographic vectors. The tracings show a shift from predominantly left ventricular activity and strain to one of right ventricular preponderance. The striking changes occur between the ages of three and eighteen months. *Right*, retouched serial electrocardiograms.

not fatigue easily, was able to keep up with her own age group and did not have exertional dyspnea. There was no history of congestive failure.

Clinical Course and Catheterization Data: On physical examination the patient appeared undernourished. There was a definite precordial bulge. The apex was felt in the fifth left interspace somewhat beyond the mid-clavicular line. There was a short, rough, grade 2 systolic murmur heard along the left sternal border not associated with a thrill. At the base there was a loud and split second sound followed by a soft, early decrescendo diastolic blow. There was no evidence of congestive failure. Fluoroscopically the heart appeared globular with a large right ventricle, no left atrial enlargement, a markedly convex main pulmonary artery, and enlarged and actively pulsatile main pulmonary arteries but clear distal lung fields.

The cardiac catheterization findings when the patient was four and five and a half years of age are detailed in Table II. It should be noted that right ventricular and main pulmonary artery pressures were essentially the same as systemic artery pressures during the first catheterization. Brachial artery pressure during the second catheterization was obtained at the end of the procedure when the patient was quite restless which accounts for the difference. A left-to-right shunt was present at the ventricular level and there was a suggestion of arterial unsaturation, thought to be due to heavy sedation. Calculation of the ratio of

TABLE II

Case 2. Large Ventricular Septal Defect. Cardiac Catheterization Data

Location	Oxygen Saturation (%)		Pressure (mm. Hg)	
	10/11/59	5/15/57	10/11/59	5/15/57
Brachial artery	91	93	80–83/57–59	124–148/96–120
Right atrium	64	70		
Right ventricle	78	77	83–86/0–1	99–102/0
Pulmonary artery	78	77	80–86/40–46	102–106/60–64
P.F./S.F.*	1.5	1.2		

* Pulmonary flow/systemic flow.

FIG. 8. Case 2. Photomicrograph of a terminal muscular pulmonary artery. Note both medial hypertrophy and intimal sclerosis. The degree of intimal change is more marked in the small vessels than in Case 1. Original magnification × 220.

systemic to pulmonary blood flow reveals that there was a decrease in pulmonary blood flow during the year and a half between the two catheterizations.

Operative and Autopsy Findings: Early surgical intervention was advised because of the pulmonary hypertension. At the time of surgery, a 2 cm. high membranous ventricular septal defect was found. This was closed without difficulty. Although the postoperative pressures were not obtained, the surgeon's impression was that the pulmonary artery pressure did not drop. During the postoperative period the balance between acute right heart failure and hemorrhagic shock was extremely difficult to maintain. The patient died twenty-four hours after surgery, the cause of death being pulmonary hypertension and right ventricular failure.

At autopsy, the right atrium and right ventricle were dilated and hypertrophied. Right ventricular thickness equalled left ventricular thickness. An analysis of lung sections revealed definite thickening of the small pulmonary vessels, due to both medial hypertrophy and intimal change (Fig. 8). There was no congestion or hemorrhage.

Comment: For reasons that are not clear, but probably related to either high pulmonary vascular tone[23] or localized areas of arteritis, this child did not pass through the phase of high output failure. Pulmonary artery flow exceeded systemic flow, but not to the extent of causing left heart failure. Her clinical course was accurately mirrored by the serial electrocardiograms accumulated during her life-time (Fig. 9). In contrast to Case 1, these demonstrate early and progressive right axis deviation. The precordial leads shifted from an initial picture of biventricular increased electrical activity to one of right ventricular hypertrophy and strain.

The surgical opinion that aortic and pulmonary artery pressures remained the same suggests that pulmonary vascular disease had advanced to a further stage than in the first patient. This is born out by the negative early history for congestive failure. Perhaps it would have been wise in this child to have created pulmonary stenosis first and then waited for a year or two before attempting closure. An alternative approach might have been the use of an artificial ductus as suggested by Sirak[24] or the use of a perforated[25] or valved[26] prosthesis to permit the more gradual adjustment to circulatory alterations.

Medium-Sized Ventricular Septal Defects

We may define a medium-sized ventricular septal defect as one which is sufficiently large to permit a volume of shunt in excess of what the lungs can handle without an increase in pressure, and yet is small enough to offer resistance to flow. The limiting effect of size means that a pressure drop across the defect from left to right ventricle must exist. Medium-sized ventricular defects may be divided into two sub-groups; the large medium and small medium. By definition, a *large medium defect* is one in which, in the early months of life, the size of the defect as compared to the size of the heart and lungs is large, and a common ejectile force exists. However, with growth, the size of defect becomes relatively less. The defect itself offers resistance to blood flow and a pressure differential between the left and right ventricles appears (Case 3).

A *small medium-sized defect* may be defined as one which in early infancy as well as in later childhood limits the shunt enough to cause a pressure differential across the defect from left to right ventricle, yet permits sufficient blood flow to embarrass the pulmonary circulation (Case 4).

Defect size is not the sole reason for a pressure

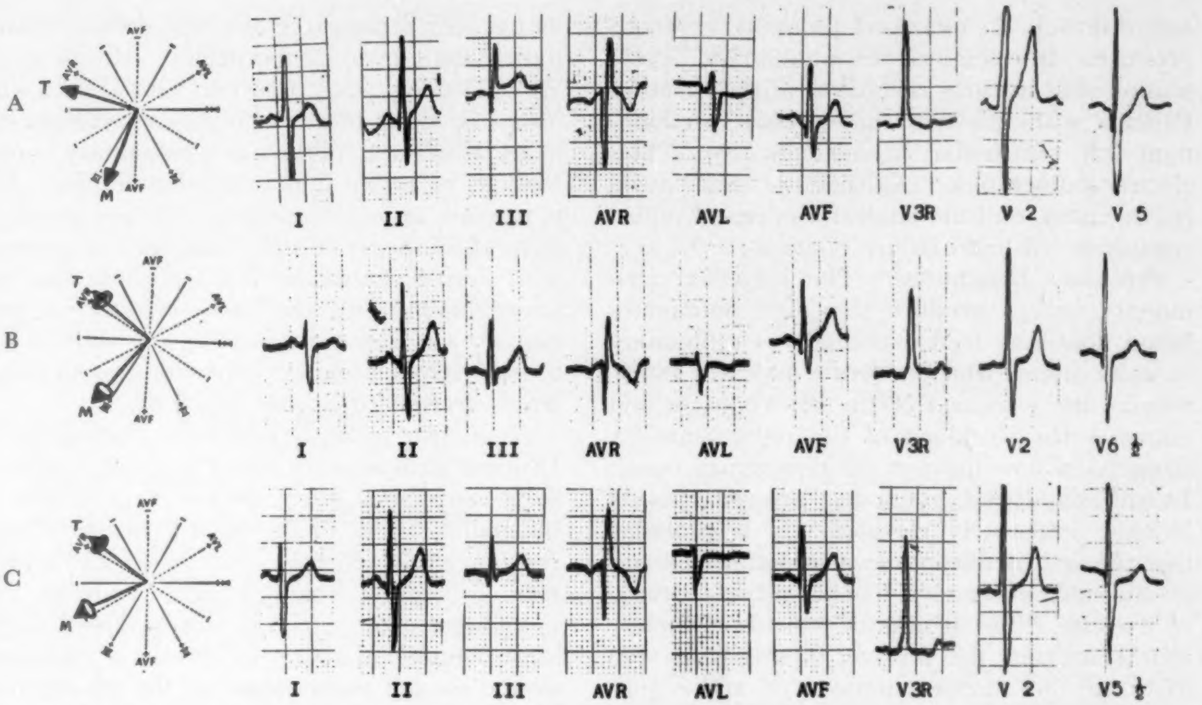


FIG. 9. Case 2. *Left*, electrocardiographic vectors. Considered as a whole, these tracings demonstrate early and progressive right axis deviation. The precordial leads shift from an initial picture of biventricular activity to one of right ventricular hypertrophy and strain. A, age eighteen months. B, age twenty-seven months. C, age forty-two months. *Right*, retouched serial electrocardiograms. A, age twenty-one months, July 22, 1953. B, age thirty-nine months, January 25, 1955. C, age fifty-four months, April 3, 1956.

gradient. Individual variations in pulmonary vasoconstrictive tone may also play a part. In one infant a high tone may limit pulmonary blood flow to such a degree that the resistance of the defect itself does not act. In another infant, with a defect of the same size, a low pulmonary vasomotor tone may permit a pulmonary blood flow sufficiently great to bring the defect resistance into play. Regardless of the exact mechanism, when a pressure gradient between ventricles does exist, the pulmonary vascular bed follows a more normal evolutionary pattern. Following birth, lumen : wall ratios increase in a more normal fashion which permits relatively high pulmonary blood flows at a low driving pressure.

In patients with large medium-sized defects signs of high output cardiac failure develop frequently. These patients closely resemble patients with a large ventricular defect. Physiologically there is no difference between the two conditions in the infant age group. In contrast, patients with a small medium-sized ventricular defect, who may also present evidence of high output cardiac failure during early infancy, have certain distinguishing findings. The presence of a pressure differential between left and right ventricles lessens the load on the right ventricle. As a consequence, the electrocardiographic and x-ray findings are primarily of left-sided enlargement. In addition, the presence of a pressure differential between left and right ventricles alters the quality and duration and intensity of the murmur. Instead of a low-pitched, relatively short, coarse systolic murmur frequently unassociated with a thrill, the murmur tends to be significantly louder, high in pitch and associated with a thrill extending throughout the major portion of systole.

Left Heart Failure or Mitral Stenosis: In the syndrome associated with the high flow, relatively low pressure septal defect, the factor of left heart failure or relative mitral stenosis is added to the clinical picture. The large shunt and high return to the left atrium may cause left ventricular failure, rise in ventricular end diastolic pressure, consequent rise in ventricular filling pressure and increased pulmonary venous pressures. In other patients, the volume return to the left atrium may be so large that the mitral valve acts as an obstruction, again leading to increased left atrial and pulmonary venous pressure. The moderate pulmonary hypertension present in childhood is primarily passive

and due only to increased pulmonary venous pressure. It resembles the pulmonary hypertension seen in early rheumatic mitral stenosis. Patients with this syndrome present predominant left ventricular enlargement, x-ray and electrocardiographic evidence of left atrial enlargement, and the clinical findings of mitral stenosis or left heart failure (Case 5).

Pulmonary Hypertension: The increased pulmonary venous pressure and high pulmonary blood flow may lead eventually to pulmonary vascular disease which in turn reduces the shunt, reduces the workload of the left ventricle and increases the workload of the right ventricle. Reversal of flow through the defect may occur. In early childhood, pulmonary arterial pressure is only moderately elevated. It is probable that the first significant elevations of pulmonary pressure come when cardiac output is increased by exercise. Just as in patients with rheumatic mitral stenosis, the passive hypertension seen early in the disease changes to active pulmonary hypertension.[23] The first indication that such a change is taking place is the shift in the electrocardiographic pattern from volume hypertrophy of the right ventricle to pressure hypertrophy, indicated by a progressive increase in the right precordial R′ and the ultimate development of the strain pattern. This, in turn, is followed by a decrease in evidence of left ventricular preponderance. Unfortunately, we do not have serial catheterization data on such a patient with a ventricular defect. However, we are publishing a case report on a small child with an aortic septal defect who progressed from left heart failure and mild passive pulmonary hypertension, to active and marked pulmonary hypertension associated with the disappearance of signs of left heart failure. Among our patients with simple ventricular septal defects, one patient demonstrates the early increase in pulmonary vascular resistance by the shift in the type of right ventricular hypertrophy seen in her serial electrocardiograms (Case 6).

TABLE III

Case 3. Medium-Sized Ventricular Septal Defect. Cardiac Catheterization Data

Location	10 Months of Age		$5^1/_2$ Years of Age	
	Oxygen Saturation (%)	Pressure (mm. Hg)	Oxygen Saturation (%)	Pressure (mm. Hg)
Right atrium	55	. . .	72	6–7/4–5
Pulmonary vein	81	. . .		
Right ventricle	70	100/0	86	47–50/3
Main pulmonary artery	74	100/80	84	50–55/15–17
Brachial artery	83	110/54	97	108–116/78–83
P.F./S.F.	3.1		1.9	

Hypertrophy of Right Ventricular Outflow Tract: In some patients with either large or medium-sized ventricular septal defects, hypertrophy of the outflow tract of the right ventricle creates resistance to blood flow to the lungs, and a pressure differential between right ventricle and pulmonary artery. Thus, the workload of the right ventricle is abnormal because of resistance to outflow and the workload of the left ventricle is abnormal because of the increased volume return to the left side of the heart. The occurrence of outflow tract hypertrophy and a pressure differential between right ventricle and pulmonary artery acts to reduce blood flow to the lungs in exactly the same manner that pulmonary vascular disease reduces blood flow to the lungs. In contrast to the latter, however, the pulmonary vascular bed is, in part, protected from progressive vascular change.

All degrees of obstruction may develop. Unfortunately for the clinician, outflow obstruction masks the classical findings and adds to the problem of proper assessment. A minor degree of outflow obstruction, high pulmonary blood flow and a medium-sized defect result in a greater workload for the left ventricle than for the right ventricle. A marked obstruction with low pulmonary flow produces more work for the right ventricle than for the left ventricle. While clinical evaluation and serial study may define ventricular workload, the distinction between pulmonary vascular disease and outflow obstruction is less easily made. It is important, therefore, to pinpoint the location of obstruction by cardiac catheterization. Furthermore, the outflow tract obstruction, because it creates a pressure gradient, alters the position, quality and duration of the systolic murmur and thus, may make a large ventricular septal defect sound like a medium ventricular septal defect. Particular attention to the intensity of the second sound may help to clarify this question (Case 7).

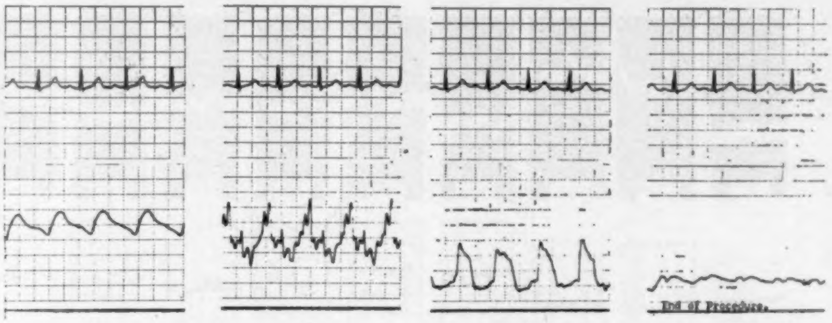


FIG. 10. Case 3, age five and a half years. Cardiac catheterization data. A, brachial artery × 20. B, pulmonary artery × 4. C, right ventricle × 20. D, right auricle × 4.

ILLUSTRATIVE CASES

CASE 3. *Change From Functionally Large to Relatively Small Defect:* This seven year old girl (S. L. H.) was found to have a murmur when five days old. During the first three months, respirations appeared normal, she ate well and gained well. Then exertional dyspnea, cardiac enlargement and growth failure developed. At ten months of age cardiac catheterization was carried out (Table III). The left atrium was catheterized through a foramen ovale. Pressures in the low right ventricle and pulmonary artery corresponded closely to those obtained from the left brachial artery. Pulmonary venous pressure was elevated which suggests left heart failure. There was a distinct increase in oxygen content in the right ventricle and pulmonary artery indicative of a left-to-right shunt at the ventricular level. Systemic arterial and pulmonary venous oxygen saturations were subnormal due, we think, to respiratory depression as well as left heart failure.

Clinical Course: When fifteen months old the patient was seen by Dr. Stanley Gibson who stated that the loud, long quality of the systolic murmur suggested a ventricular septal defect. Her course then improved. Evidence of dyspnea disappeared, growth and development became normal and she was able to keep up with children her own age. On physical examination at age twenty-seven months, she appeared well developed and well nourished. There was no cyanosis. There was a definite precordial bulge. The cardiac apex was palpable in the fifth left interspace beyond the nipple line. There was a diffuse systolic thrill and a loud, moderately high-pitched, long systolic murmur heard maximally in the fourth left interspace. The pulmonary second sound was accentuated and split. An apical mid-diastolic rumble was present. There was no evidence of congestive failure. X-ray examination revealed an enlarged left ventricle and atrium and hypervascular lung fields.

The patient was seen again at age four. She was fully active showing only mild fatigue with severe exercise. The murmur was now higher pitched, and more jet-like in character. The pulmonary second sound was split, but not accentuated. The mid-diastolic rumble was no longer heard. The heart did not appear as large, or the lung fields as vascular as they had been.

Cardiac catheterization was repeated at age five and a half years (Fig. 10). A remarkable drop in pulmonary artery pressure and a decrease in the ratio of pulmonary to systemic blood flow was demonstrated. There was a small pressure gradient between the main body of the right ventricle and the pulmonary artery.

A lung biopsy specimen revealed moderate pulmonary vascular changes, primarily medial hypertrophy. There was little or no evidence of intimal

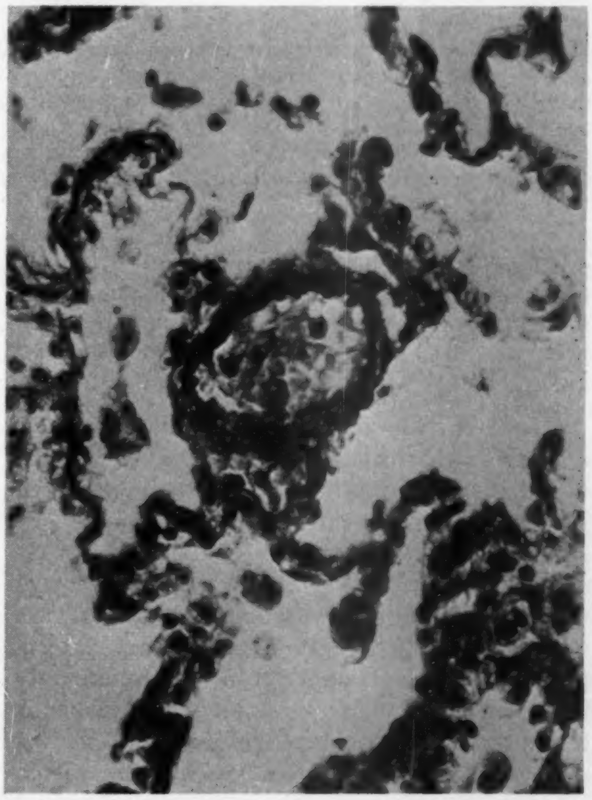


FIG. 11. Case 3. Photomicrograph of small muscular pulmonary artery. Note the medial hypertrophy but relatively large lumen size. Original magnification × 640.

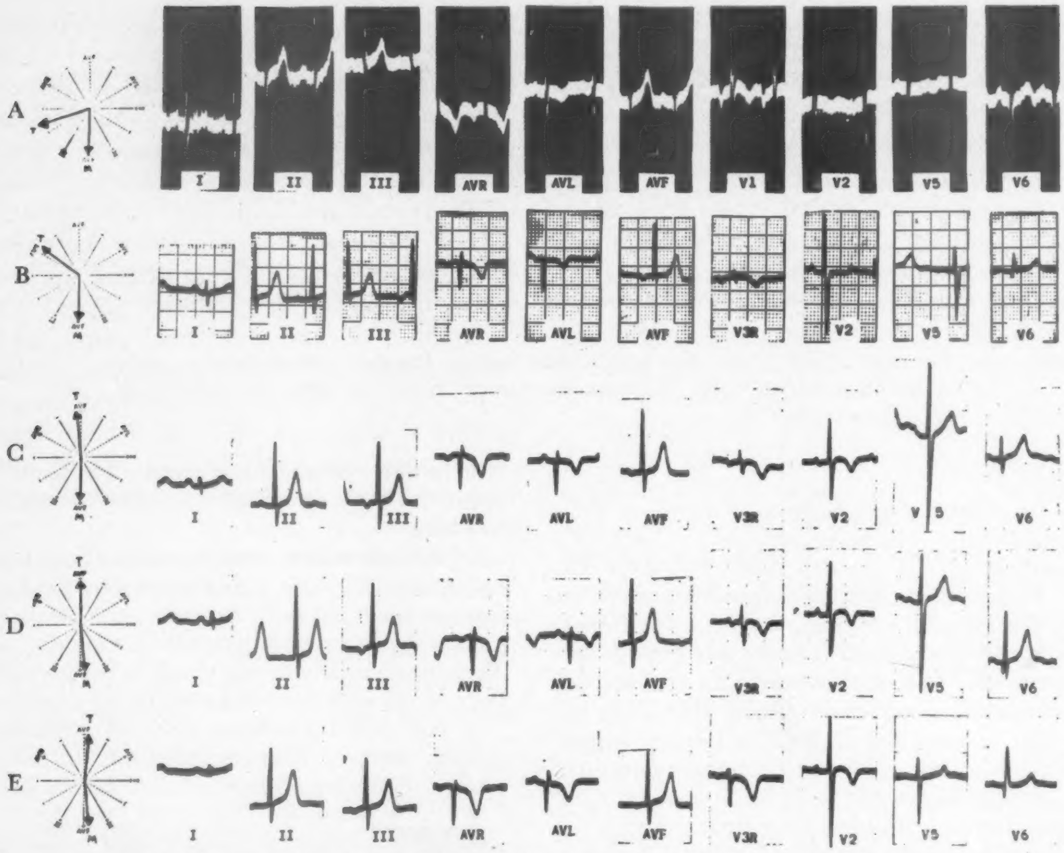


FIG. 12. Case 3. *Left,* electrocardiographic vectors. There is a slight shift of the mean QRS vector to the left associated with a more marked shift of the terminal vector. The precordial leads suggest an increase in left ventricular activity, but show definite evidence of persistence of increased right ventricular activity. A, age thirteen months. B, age fifty-one months. C, age fifty-eight months. D, age seventy months. E, age seventy-nine months. *Right,* retouched serial electrocardiograms. A, age thirteen months, November 6, 1952. B, age four years, January 26, 1956. C, age four and a half years, August 3, 1956. D, age five and a half years, August 22, 1957. E, age six years, April 11, 1958.

proliferation. The lumen was not as large as it would be in a normal subject but it was considerably greater than in patients with severe pulmonary hypertension. A typical small pulmonary artery is shown in Figure 11.

Comment: The defect in this child was large enough so that during early infancy the course was that of a common ventricular ejectile force. However, with growth the defect became progressively less significant. The size of the defect itself limited the volume of flow to a level which the pulmonary vascular bed could handle without a marked rise in pulmonary arterial pressure. This change from a functionally large defect to a relatively small defect was manifest in the patient's clinical course.

Several findings suggested that the defect was medium in size. The early period of high output cardiac failure was followed by progressive and marked improvement. The murmur, as described first by Dr. Gibson, was loud and long, high-pitched, and was associated with a thrill. Such a murmur suggests a pressure gradient. The fact that the murmur was loudest in the fourth left interspace argued against pulmonary stenosis. An analysis of her serial electrocardiograms (Fig. 12) indicated biventricular stress in infancy which shifted to greater left ventricular preponderance with the passage of time.

Small medium-sized defects are characterized by the presence of a pressure gradient across the defect from left to right ventricle appearing soon after birth. Patients with these defects also may have a stormy neonatal course and then improve as growth makes the defects even less significant.

CASE 4. *Medium-Sized Defect With Pressure Gradient Across Defect and Stormy Neonatal Course:* This four and a half year old child (J. A. L.) weighed 5 pounds 7 ounces at birth and 9 pounds when she was seven

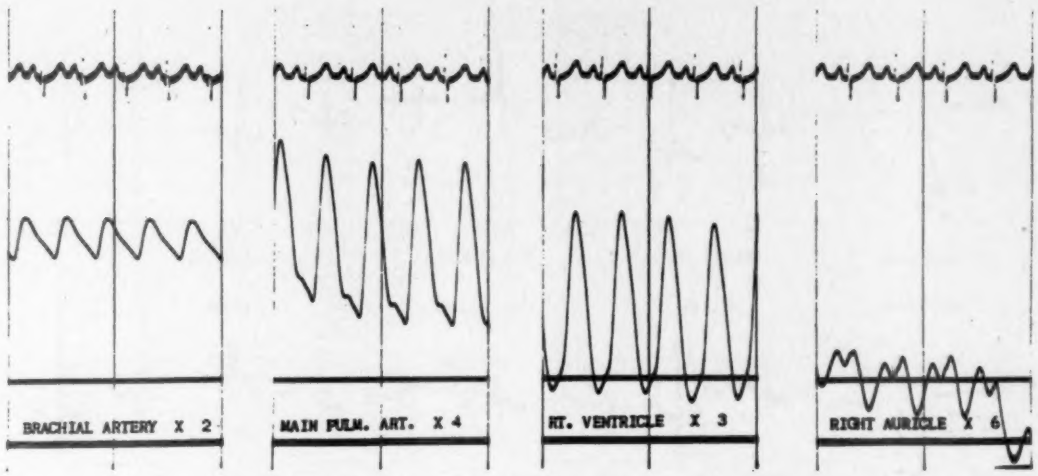


FIG. 13. Case 4. Serial cardiac catheterization data.

months old. Marked shortness of breath and ease of fatigue first developed at two weeks of age. Respiratory and pulse rates remained rapid. Perspiration was marked. She appeared chronically ill and undernourished. The chest was barrelshaped. There was a slight precordial bulge. The apex was in the fifth and sixth interspaces in the anterior axillary line. During severe crying there was a moderately short, but loud systolic murmur maximal close to the sternum in the fourth left interspace. When the baby quieted down the murmur became longer, higher pitched and harsh. There was an apical mid-diastolic rumble. The pulmonary second sound was loud and split. There were fine rales over both sides of the chest posteriorly; the liver was palpable 2 fingerbreadths below the right costal margin. The skin over the extremities felt thick which suggested peripheral edema. X-ray examination revealed marked cardiac enlargement involving all chambers. The lung fields were hypervascular.

First Catheterization Findings: The baby was admitted to the hospital, digitalized and then catheterized. The results of this catheterization are listed in Table IV. The right ventricular and pulmonary artery pressures were essentially the same and although elevated, they were only about 50 per cent of systemic arterial pressure. Since there was no evidence of an increase in oxygen content in the right atrium, the foramen ovale was thought not to be functionally patent. There was a marked step-up in oxygen content in the pulmonary artery and high right ventricle. Oxygen unsaturation of the pulmonary venous and left ventricular blood was present, probably due to the presence of pulmonary edema and depressed respirations.

Subsequent Clinical and Catheterization Findings: The baby improved and during the next six weeks gained $1^3/_4$ pounds. When seen a year later, respirations were quiet, exercise tolerance improved. The heart did not appear to be as large. The apical mid-diastolic rumble had disappeared. The systolic murmur was now longer, louder and harsher than at the time of the first examination and obscured the second sound.

When cardiac catheterization was repeated at age four and a half years, the main pulmonary artery pressure was at the upper limits of normal. There was a slight pressure gradient across the pulmonary valve. The arterial oxygen saturation was normal. There was a step-up in oxygen content in the main pulmonary artery and right ventricular outflow tract consistant with the diagnosis of a ventricular septal defect.

Operative Findings: At the time of corrective surgery a defect measuring 6 to 7 mm. in diameter and high in the membranous septum was found. This was closed without difficulty. The patient's postoperative course was uneventful.

Comment: In this child, although the period of

TABLE IV

Case 4. Small Medium-Sized Ventricular Septal Defect. Cardiac Catheterization Data

Location	7 Months of Age		$4^1/_2$ Years of Age	
	Oxygen Saturation (%)	Pressure (mm. Hg)	Oxygen Saturation (%)	Pressure (mm. Hg)
Brachial artery	...	...	96	76–77/58
Pulmonary vein	81	7–12/0–7	...	...
Main pulmonary artery	77	35/14	80	26–34/5–11
Right ventricle	72	35–42/4	70	40–45/0
Right atrium	60	...	72	1/0
P.F./S.F.	5.2	...	1.4	...

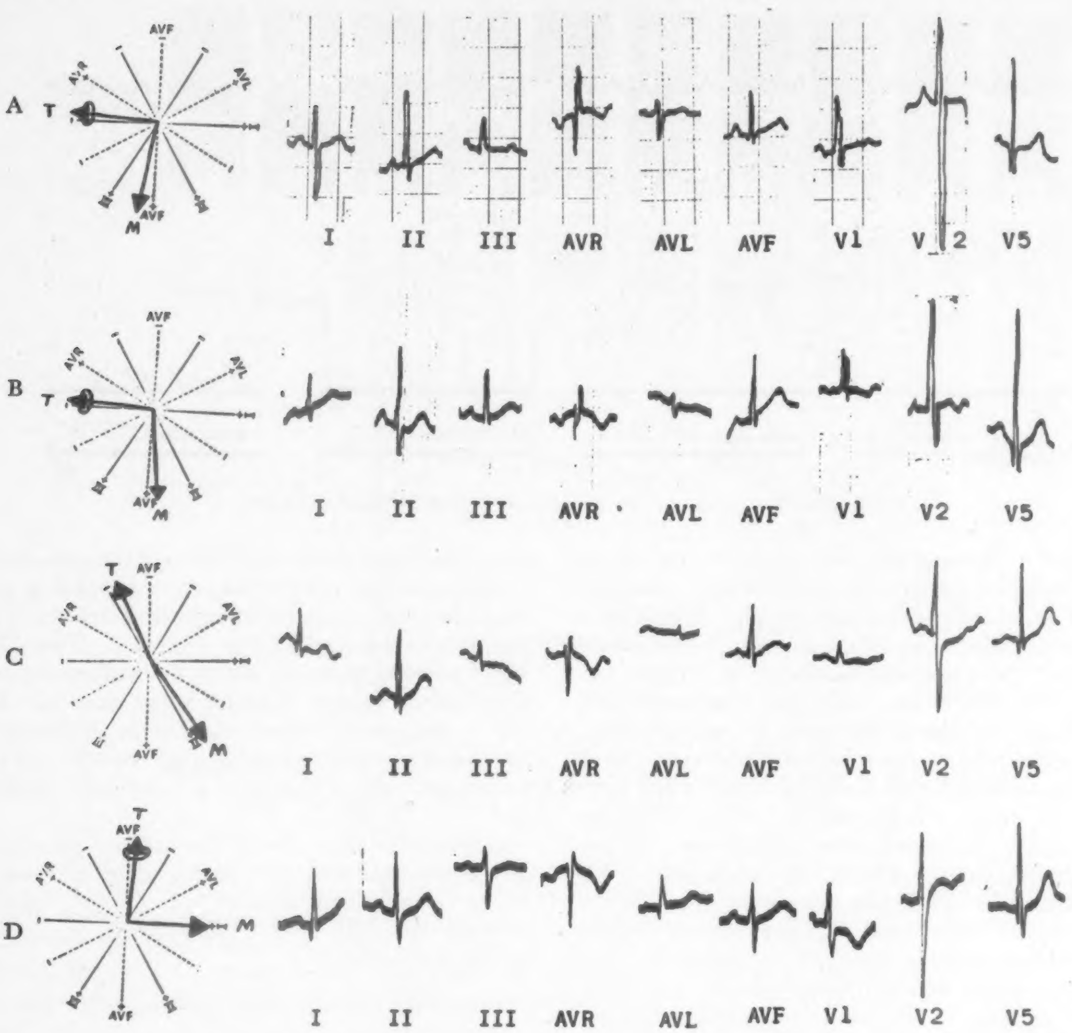


FIG. 14. Case 4. *Left*, electrocardiographic vectors. Serial tracings demonstrate rotation of the mean QRS vector from plus 100 degrees to 0 degrees, indicating progressive increase in left ventricular activity. The changes in the precordial leads are characterized by a change from a biventricular pattern to one of predominant left ventricular activity. A, age seven months. B, age twenty months. C, age thirty-three months. D, age forty-seven months. *Right*, retouched serial electrocardiograms. A, age seven months, April 1, 1955. B, age nineteen months, April 26, 1956. C, age thirty-two months, May 20, 1957. D, age forty-six months, July 29, 1958.

infancy was stormy, there still was a pressure gradient across the defect indicating that the volume of blood flow through the defect was limited. The presence of a significant pressure gradient across the defect in infancy, proved by catheterization, was suggested by the quality, length and intensity of the systolic murmur and thrill. It also was suggested by an analysis of serial electrocardiograms which demonstrated rotation of the mean QRS vector from +100 to 0 degrees, indicating progressive increase in left ventricular electrical activity (Fig. 14). The changes in the precordial leads are characterized by a shift from a biventricular pattern to one of predominant left ventricular activity.

CASE 5. *Large Left-to-Right Shunt and Functional Mitral Stenosis:* In this ten year old boy (J. D.) a loud systolic murmur was heard over the precordium shortly after his birth. He had pneumonia once during the first year and his growth was poor. Some dyspnea and ease of fatigue were present. During examination at the age of ten a definite precordial bulge and increased precordial activity were noted. The apex beat was easily felt in the seventh interspace in the anterior axillary line. A strong systolic thrill was felt maximal in the third and fourth left interspaces and associated with a long, loud, high-pitched, systolic murmur. The second heart sound was split and somewhat accentuated. An apical mid-diastolic rumble was present. There was no evidence of congestive failure. X-ray examination revealed marked enlargement of the left ventricle, moderate right ven-

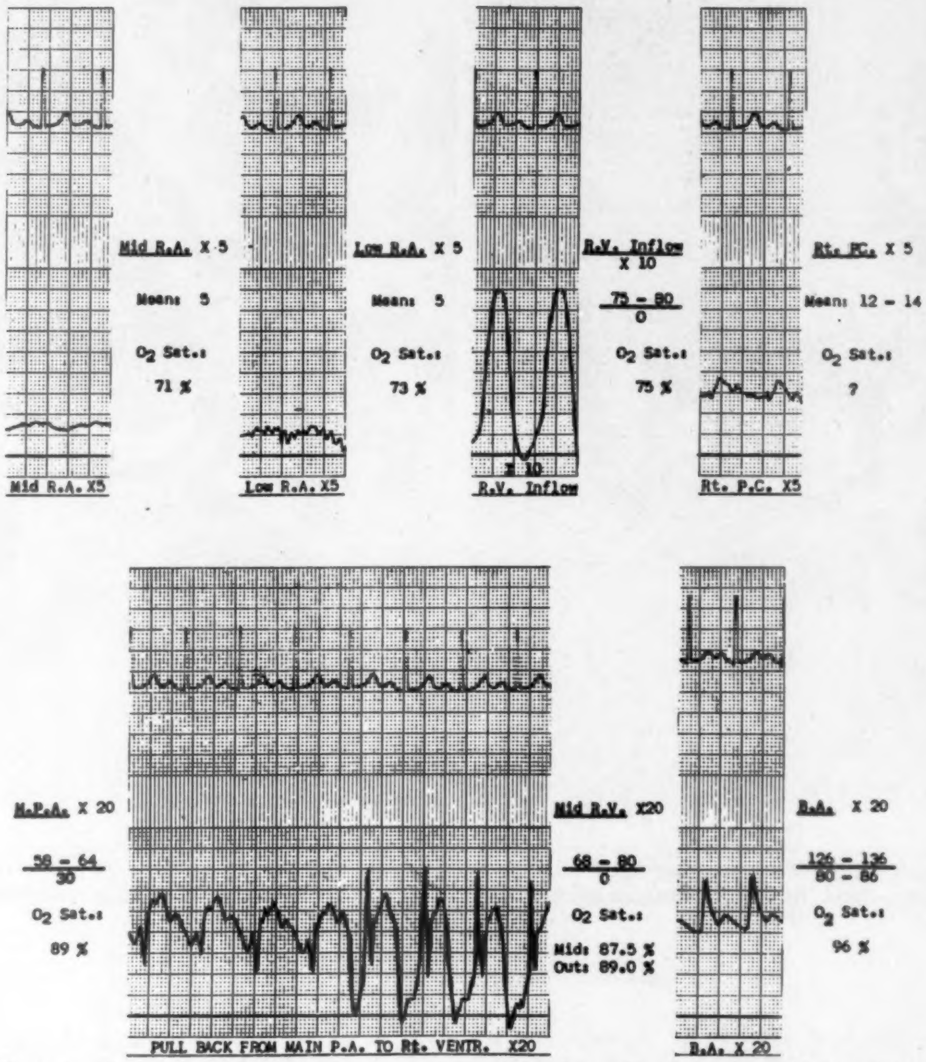


FIG. 15. Case 5. Medium-sized ventricular septal defect. Cardiac catheterization data.

tricular and left atrial enlargement and hypervascular lung fields.

Catheterization Findings: The results of cardiac catheterization are given in Figure 15. There was a marked increase in oxygen content in the right ventricular outflow tract, and no evidence of a right-to-left shunt. Right ventricular and pulmonary artery pressures were both elevated, although a slight pressure gradient existed between the mid-right ventricle and main pulmonary artery segment. Mean pulmonary capillary pressure measured 12 to 14 mm. Hg. The findings were consistent with a medium-sized ventricular defect, a marked left-to-right shunt, and moderate pulmonary arterial and venous hypertension.

Operative Findings: A high ventricular septal defect measuring approximately 1 cm. in diameter was found at surgery. Closure of the defect produced complete heart block which did not respond to either Isuprel® therapy, partial perfusion, or the electronic pacemaker.

Autopsy examination revealed a normal mitral valve measuring 85 mm. in circumference, a tricuspid valve measuring 80 mm. in circumference and the largest left atrium and left ventricle we have seen in patients with simple ventricular septal defects. Left ventricular thickness was 15 mm. and right ventricular thickness was 5 mm. There was pulmonary hemorrhage and congestion. Examination of the microscopic sections of the lungs revealed marked thickening of the small and large pulmonary veins, moderate capillary dilatation and moderate thickening of the pulmonary arterioles (Fig. 16).

Comment: In this patient, the defect in early infancy was a large medium-sized defect with a large left-to-right shunt. The size of this defect increased so that the shunt increased steadily as the child grew. Passive dilatation of the pulmonary vessels occurred without progressive pulmonary vascular disease. The high pulmonary blood flow produced a functional mitral stenosis, elevation of pulmonary venous pressure and pulmonary venous morphologic change.

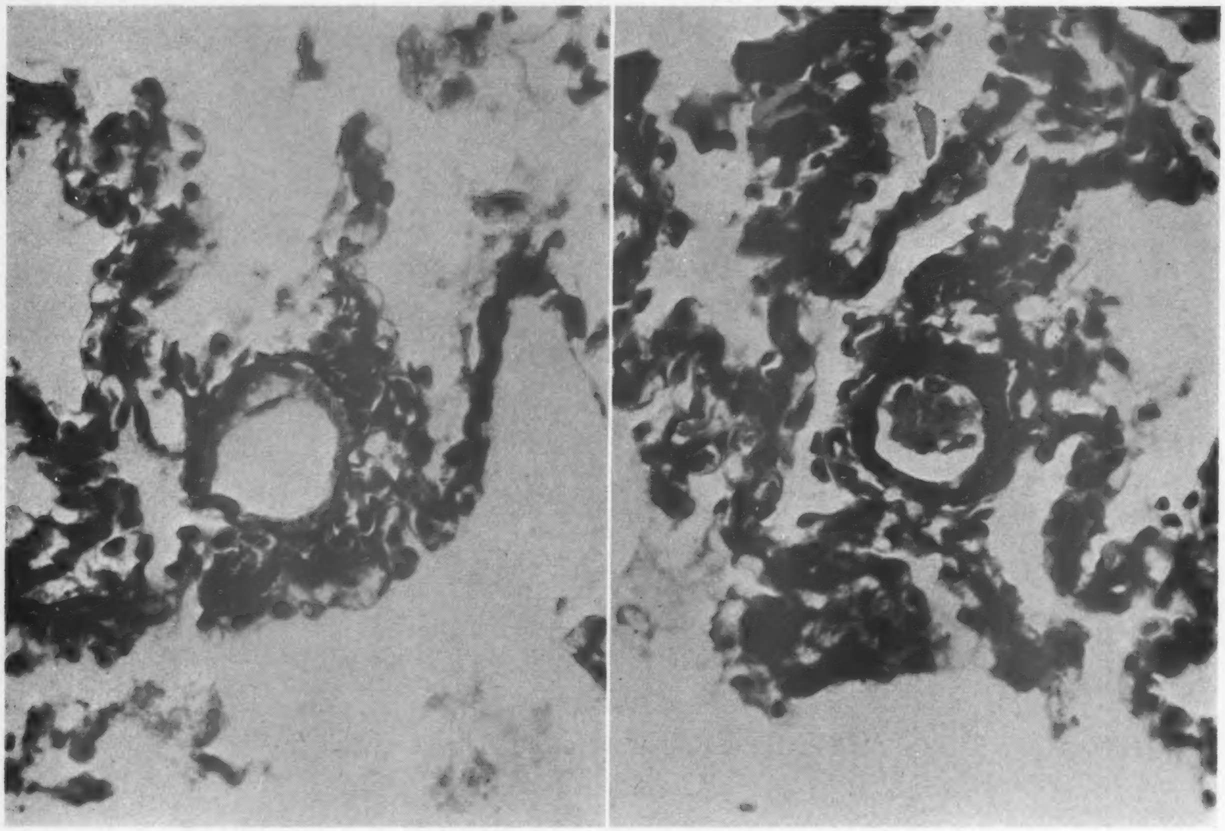


FIG. 16. Case 5. A, photomicrograph of a small pulmonary vein. Note the rather severe intimal sclerosis. B, small muscular artery. Note the moderate medial hypertrophy and early intimal change. Original magnification × 720.

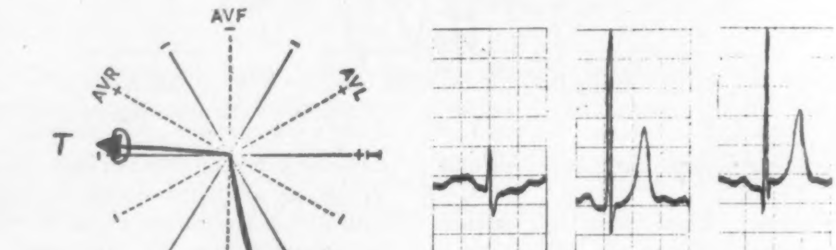


FIG. 17. Case 5. Electrocardiographic vector. Age eleven years, mean QRS vector is normally directed. P wave changes indicate left auricular enlargement. The precordial leads show patterns of diastolic overload of both ventricles, most marked over the left. Retouched electrocardiograms.

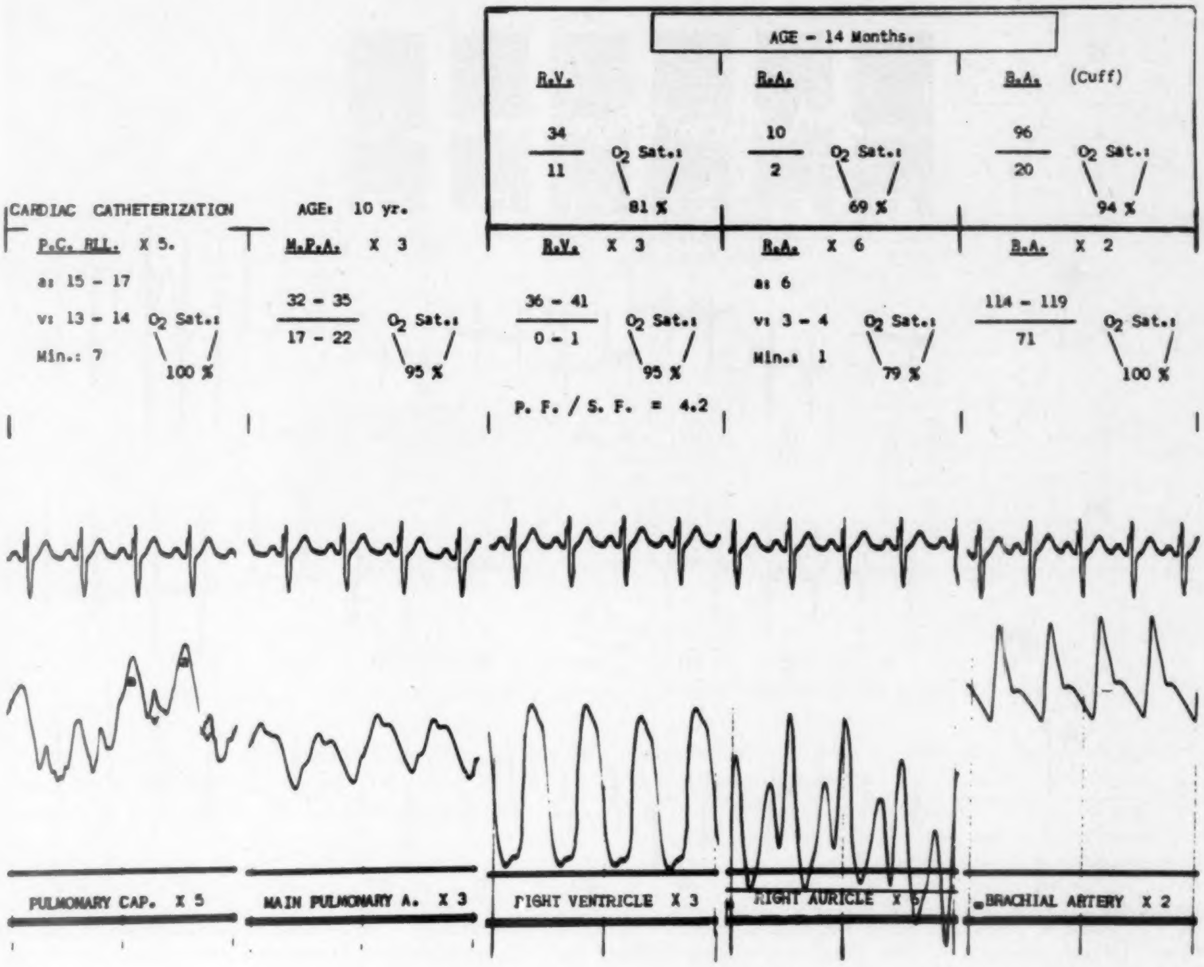


FIG. 18. Case 6. Serial cardiac catheterization data.

Serial electrocardiograms are not available in this patient. In the single tracing the mean QRS vector was normally directed. P wave changes indicated left atrial enlargement. The precordial leads showed patterns of volume overload of both ventricles most marked over the left side (Fig. 17).

CASE 6. *Large Shunt With Increasing Right Ventricular Preponderance:* This ten year old child (E. D. P.) was found to have a heart murmur at the age of six months. The murmur was described as loud, systolic in time and heard all over the precordium. X-ray examination revealed marked cardiac enlargement and increased pulmonary vascular markings. At one year the patient was hospitalized because of acute heart failure and pneumonia. She was rehospitalized at fourteen months. Then she appeared chronically ill and dyspneic. There was a precordial bulge; the apex was visible in the sixth left interspace in the anterior axillary line. There was a marked systolic murmur and thrill, loud and harsh, maximal in the fourth left interspace. An apical diastolic rumble was present. X-ray examination revealed marked enlargement of the left ventricle and atrium. The cardiothoracic ratio was 64 per cent. The lung fields appeared vascular.

Cardiac catheterization (Fig. 18) indicated a left-to-right shunt at the ventricular or great vessel level, and moderate right ventricular hypertension. Arterial saturation was normal. Arterial pressure by cuff was 90/20. Despite the absence of concrete evidence of patent ductus arteriosus, the high pulse pressure was considered significant enough to warrant exploratory thoracotomy. No ductus was found. Convalescence was uneventful.

Subsequent Course and Findings: The patient was not seen again until the age of nine when she complained of some ease of fatigue and definite exertional dyspnea. The cardiac apex was in the seventh left interspace in the anterior axillary line. There was increased precordial activity, predominantly over the apex. A long, coarse, loud systolic murmur and thrill were present along the left sternal border. A mid-diastolic rumble was heard at the apex. The pulmonary second sound was split and moderately loud. There was no evidence of congestive failure.

A year later she was recatheterized because of the

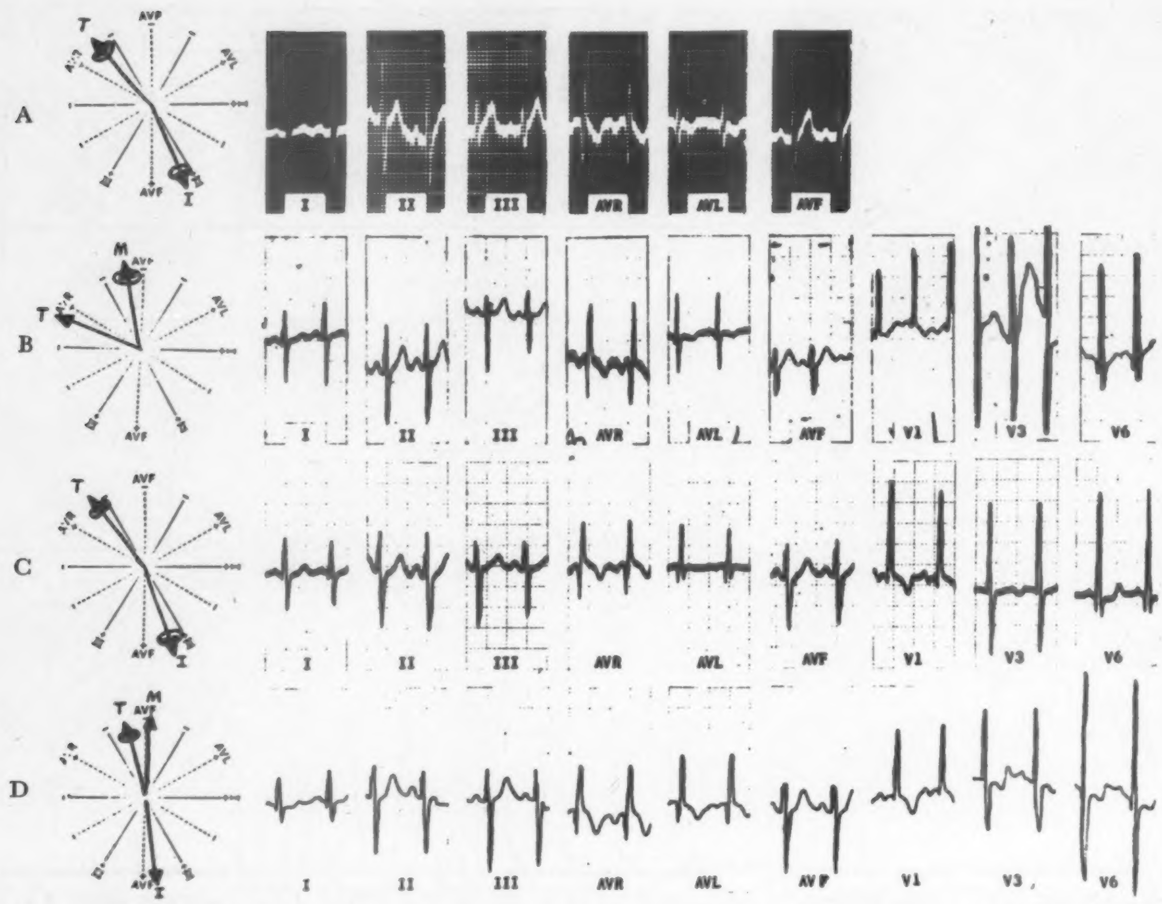


FIG. 19. Case 6. *Left*, electrocardiographic vectors. A, age eleven months. B, age seventeen months. C, age six years. D, age nine years. The tracings available indicate an initial pattern of biventricular activity which persists. This is associated with evidence of increasing right ventricular preponderance and strain. *Right*, retouched serial electrocardiograms. A, age eleven months, March 2, 1950. B, age seventeen months, September 6, 1950. C, age six years, June 8, 1955. D, age ten years, March 9, 1959.

progression of ease of fatigue and exertional dyspnea. A large left-to-right shunt at the ventricular level was demonstrated. There was some pulmonary hypertension and no right ventricular outflow tract obstruction. Serial electrocardiograms (Fig. 19) indicated an initial pattern of biventricular activity which persisted. This was associated with evidence of increasing right ventricular preponderance and strain and a shift in the form of right ventricular stress from a volume load to a pressure load pattern.

Operative Findings: The increase in symptoms, large shunt and electrocardiographic evidence of increasing right ventricular pressure load, made surgical correction of the defect advisable. This was carried out and a defect measuring over 1 cm. in diameter was found and closed. Following closure there was a prompt drop in pulmonary artery pressure to normal.

Comment: Despite the fact that pulmonary artery pressure was not elevated to any great degree at the time of either catheterization, the increase in symptoms and evidence of a change in workload of the right ventricle in the electrocardiogram suggested that at times pulmonary pressure was elevated, and that the patient was approaching the stage of significant pulmonary vascular disease. Analysis of the lung biopsy specimen obtained at the time of surgery revealed dilatation of most of the arterial bed, but in some areas, early intimal change was present, superimposed on a relatively thick-walled media. It is our belief that progressive pulmonary vascular disease would have developed in this child if the stress on the lungs had not been removed by closure of the defect.

CASE 7. *Obstruction of Right Ventricular Outflow Tract:* This four year old child (E. K.) was first hospitalized for recurrent and severe pulmonary infections at the age of six months. At that time the heart was greatly enlarged, and a loud systolic murmur was present over the precordium. He was readmitted at two years of age because of cardiac failure. He was digitalized with subsequent improvement in dyspnea, a decrease in neck vein distention, a slower heart rate

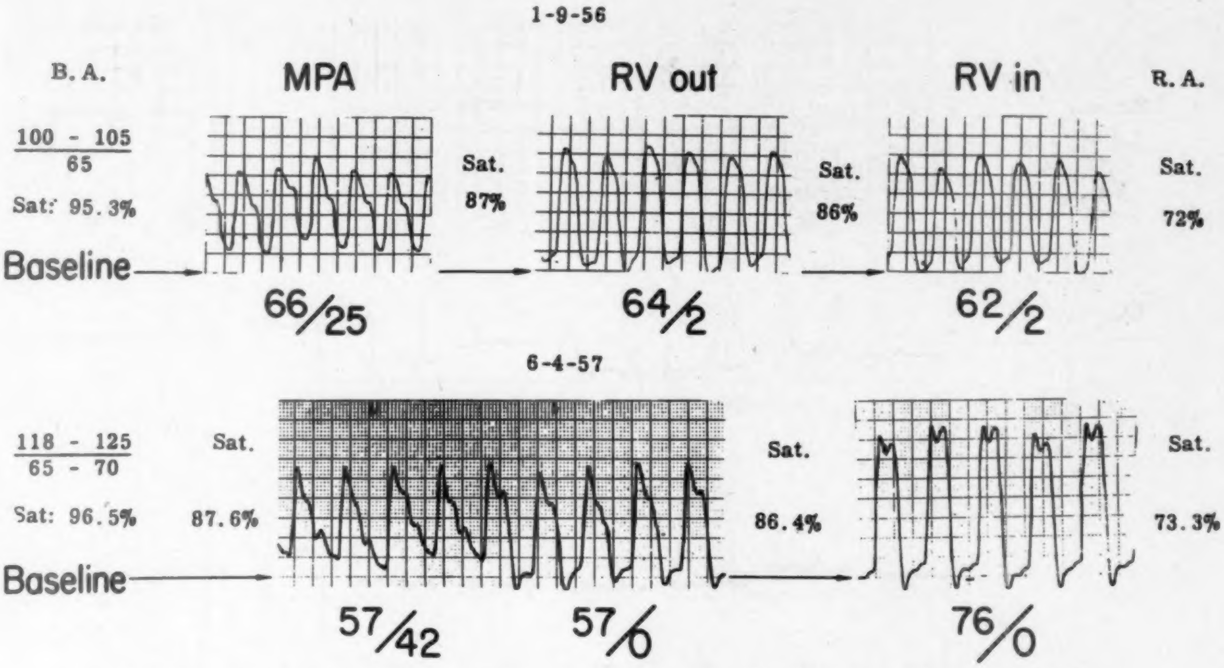


FIG. 20. Case 7. Medium-sized ventricular septal defect. Serial cardiac catheterization data.

and a liver edge palpable only 1 fingerbreadth below the right costal margin instead of 4. The apex of the heart was in the fifth left interspace in the anterior axillary line. There was a precordial bulge and a forceful second thrust. Maximal in the fourth left interspace there was a moderately loud, long, systolic murmur accompanied by a thrill. An apical mid-diastolic rumble was heard. The pulmonary second sound was definitely split and accentuated. X-ray examination revealed gross cardiac enlargement involving all chambers. The lung fields appeared vascular.

Cardiac catheterization was carried out (Fig. 20) and the findings suggested right ventricular and pulmonary artery hypertension.

Clinical Course and Recatheterization Findings: During the next few years the patient showed steady improvement. Evidence of cardiac failure decreased although heart size still remained large. The murmur did not change. The pulmonary second sound remained loud and split. Because the pulmonary second sound appeared to be increasing in intensity he was recatheterized when forty-three months old.

In contrast to the first catheterization, the second catheterization revealed a distinct pressure gradient between the right ventricle and pulmonary artery. Right ventricular pressure was higher than on the previous catheterization and pulmonary artery pressure definitely lower. The ratio of pulmonary and systemic flow remained essentially unchanged.

Operative Findings: At the time of surgery a moderate-sized ventricular septal defect was found and closed using an Ivalon® patch. The outflow tract of the right ventricle was observed to be hypertrophied but no clear-cut area of stenosis was noted. The reduction in pulmonary blood flow following closure of the defect abolished the pressure differential from right ventricle to pulmonary artery. His postoperative course was complicated by a transfusion reaction and was terminated by a perforated gastric ulcer.

Comment: In less than two years a significant pressure gradient between right ventricle and pulmonary artery developed. This gradient probably resulted from two changes: (1) gradual hypertrophy of the outflow tract of the right ventricle reduced outflow lumen size and (2) since pulmonary blood flow gradually increased, the point was reached where obstruction became significant and a pressure gradient appeared. We misinterpreted the progressive right ventricular preponderance in the electrocardiogram (Fig. 21) and the increasing pulmonary second sound as being caused by progressive pulmonary vascular disease. Cardiac catheterization demonstrated that the obstruction was in the outflow tract and not the small pulmonary vessels. Cardiac catheterization is frequently the only method of determining whether right-sided obstruction exists in the small arteries or the outflow tract of the right ventricle.

SMALL VENTRICULAR SEPTAL DEFECT

A small ventricular defect may be defined as one which so limits flow through the defect that the lungs are completely capable of handling the blood flow without an increase in pulmonary

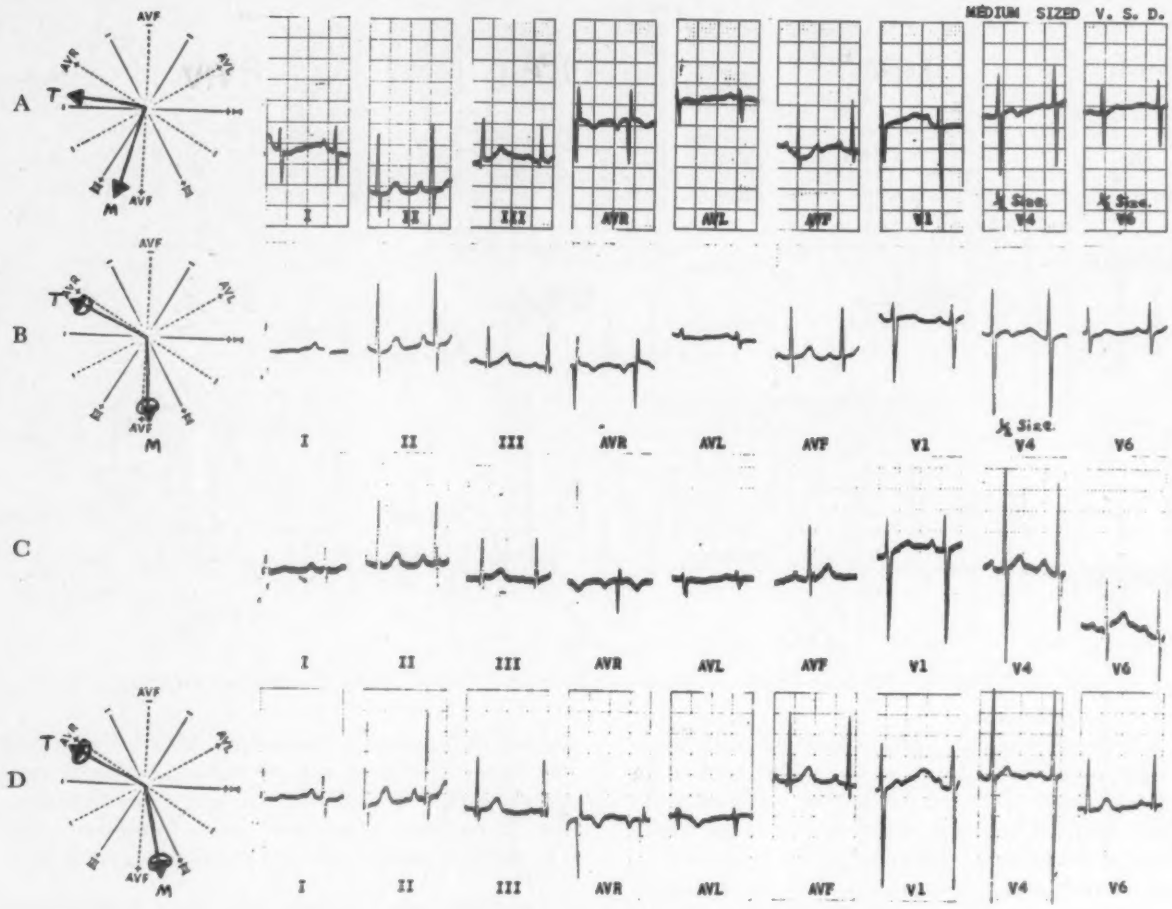


FIG. 21. Case 7. *Left*, electrocardiographic vectors. A, age twenty-five months. B, age thirty-five months. D, age forty-nine months. The mean QRS vector shifts from the picture of right axis deviation to normal. The precordial leads indicate a persistent pattern of biventricular activity but show definite evidence of increasing left ventricular preponderance. *Right*, retouched serial electrocardiograms. A, age twenty-five months, December 8, 1955. B, age thirty-five months, October 4, 1956. C, age thirty-nine months, February 25, 1957. D, age forty-nine months, December 2, 1957.

artery or right ventricular pressure. The left ventricle has only a slightly increased workload since the shunt is small. Symptoms are minimal or totally absent, although there may be poor weight gain and susceptibility to infection in early infancy. There is no bulge to the precordium and the heart appears only slightly enlarged if at all to percussion.

The characteristic physical findings are a loud, high-pitched, long, systolic murmur associated with a thrill, not associated with an accentuated and split pulmonary second sound or with an apical mid-diastolic rumble. Evidence of cardiac failure is lacking. Roentgenograms usually reveal slightly increased vascularity of the lung fields and minimal left ventricular enlargement. As a rule the left atrium is normal. The characteristic finding in serial electrocardiograms is the relatively early appearance of the normal adult pattern of left ventricular preponderance, without evidence of hypertrophy of either ventricle.

CASE 8. *Small Septal Defect With Normal Pressures:* This seven year old boy (R. F.) was noted to have a heart murmur at the time of his first pediatric examination. His neonatal course was normal as were his growth and development. There was no history of cyanosis, exertional dyspnea, orthopnea or increased susceptibility to respiratory infections. He was an obese youngster with good color, normal respiratory rate and no evidence of congestive failure. There was no precordial bulge and the precordium was quiet. Maximal precordial activity was felt at the apex. The heart did not appear to be enlarged. There was a high-pitched, systolic murmur which was jet-like in quality and at times associated with a palpable systolic thrill, maximal in the fourth left interspace. Pulmonary second sound was slightly split, but not accentuated. A mid-diastolic rumble was not heard.

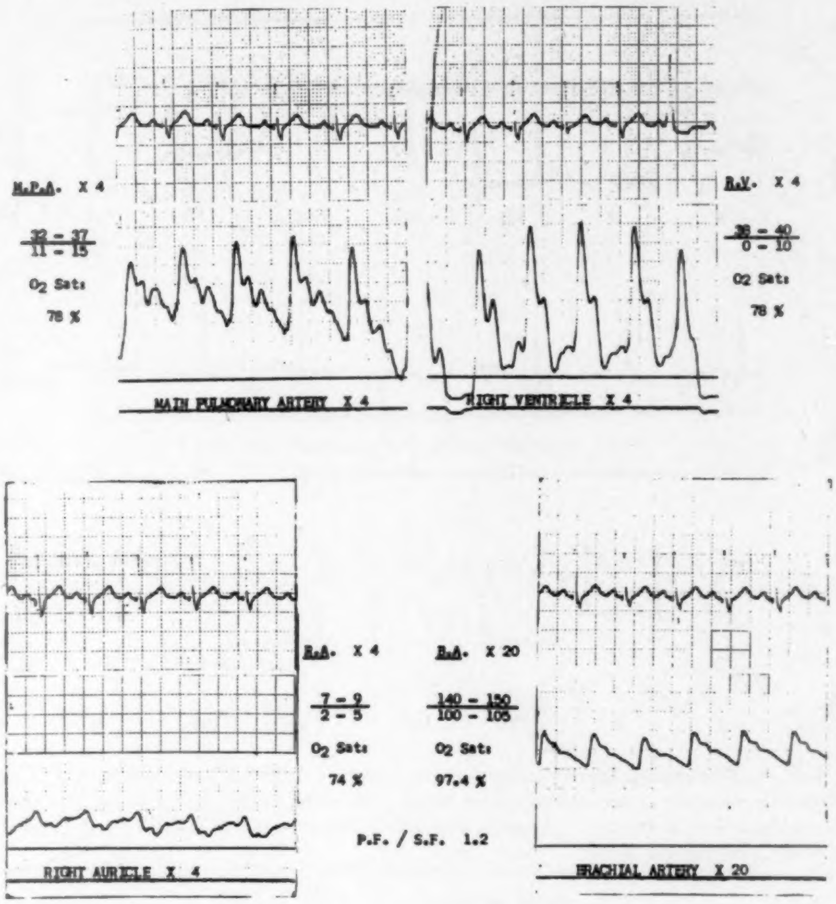


FIG. 22. Case 8. Small ventricular septal defect. Cardiac catheterization data

X-ray examination revealed moderately prominent vascular markings in the lung fields, and a rather globular-shaped heart which suggested left ventricular enlargement.

Cardiac catheterization (Fig. 22) revealed a ratio of systemic to pulmonary blood flow of 1:2. There was a slight increase in oxygen content in the right ventricle. Pulmonary artery pressures were at the upper limits of normal. Peripheral arterial saturation and pressures were normal.

Comment: This child's course suggested that the defect at no time placed a significant load on the pulmonary circulation or the heart. The quality, duration and amplitude of the murmur suggested a small or medium-sized defect. Serial electrocardiograms failed to reveal any definite abnormality, except perhaps, for an increase in amplitude of the QRS complex across the left chest leads (Fig. 23). The pattern was that of a normal adult.

The diagnosis in this patient has not been proved, since it seems unwise to advise surgery in the presence of such normal findings.

Ventricular Defects of the Muscular Septum

Defects of the muscular septum tend to be multiple and anatomically large, but functionally small. As Edwards[7] has observed in early infancy such defects appear ovoid in shape whereas later on they tend to lengthen out so that the edges almost approximate. Major flow through a ventricular defect occurs during systole at a time when the muscle mass of ventricular septum is contracted. Since the defect is surrounded by muscle, contraction of septal muscle must produce an actual decrease in size of the defect. Thus, large muscular ventricular septal defects physiologically behave as medium or even small ventricular defects.

CASE 9. *Large Muscular Defect With Large Shunt and Pressure Gradient Across Defect:* This eight year old child (J. A. R.) weighed 8 pounds 2 ounces at birth and 9 pounds 5 ounces at five months of age. A murmur was heard during her first hospitalization when three months old. Repeated pulmonary infections,

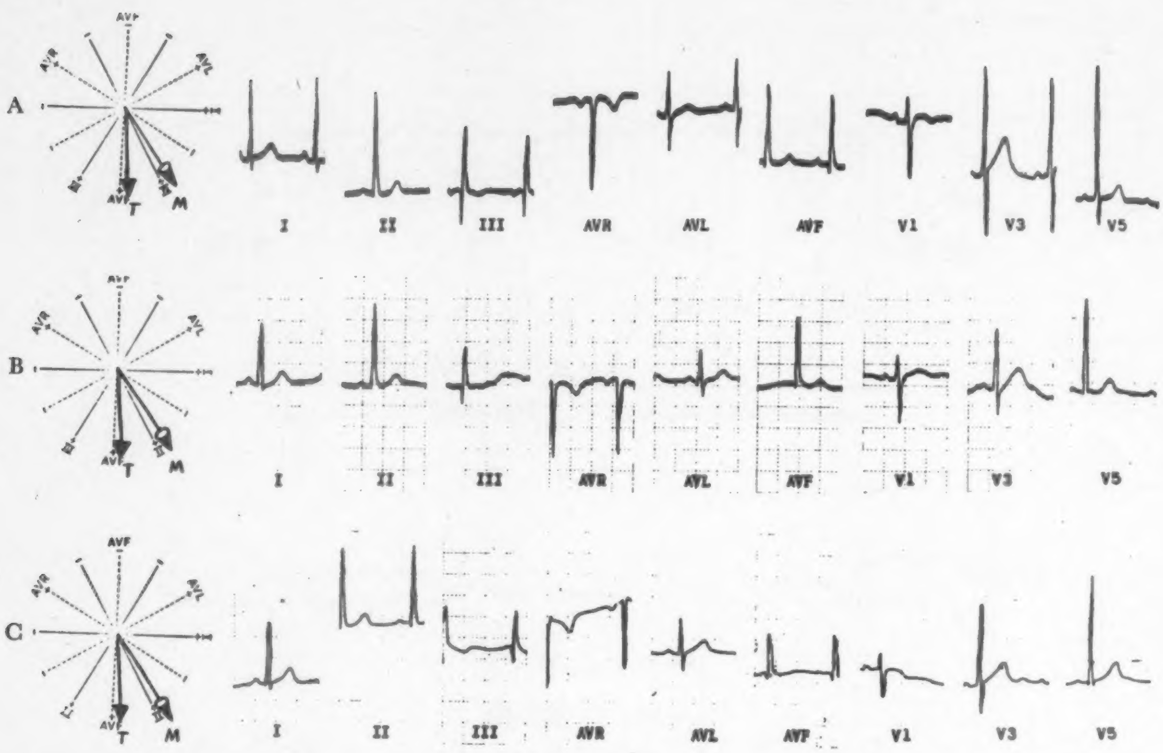


Fig. 23. Case 8. *Left*, electrocardiographic vectors. A, age seven years. B, age eight years. C, age nine years. Although the left ventricular complexes are at the upper limits of normal in the first tracing, the remainder are normal. *Right*, retouched serial electrocardiograms. A, age seven years, November 16, 1956. B, age eight years, February 24, 1958. C, age nine years, February 6, 1959.

rapid respirations and ease of fatigue were most marked in early infancy, but persisted throughout the patient's life. Cyanosis was not noted. She appeared small and underdeveloped. There was no cyanosis. There was a marked precordial bulge and marked precordial activity. A strong apical impulse was palpable in the sixth interspace in the anterior axillary line. There was a moderately high-pitched, loud, long, systolic murmur, heard best over the lower sternum and accompanied by a systolic thrill. An apical mid-diastolic rumble was present. The pulmonary second sound was accentuated and split. There was no evidence of failure. X-ray examination showed enlargement of all chambers and vascular appearing lung fields.

Catheterization Findings: The results of cardiac catheterization (Fig. 24) indicated a marked increase in oxygen content in the outflow tract of the right ventricle and pulmonary artery. Arterial oxygen saturation and blood pressure were within normal limits. Right ventricular and pulmonary pressures were greater than 50 per cent of systemic pressure.

Operative Findings: At the time of surgery a single defect measuring 2.5 cm. in diameter was found in the muscular septum. It was closed using an Ivalon sponge prosthesis. Cardiac rhythm remained normal throughout. The postoperative course was complicated by the development of bronchopneumonia terminating fatally.

Autopsy confirmed the clinical impression that both ventricles were under stress. No other defects were present. Examination of the lungs revealed moderate medial hypertrophy and minimal intimal proliferation of the small arteries, capillary and venous congestion (Fig. 25).

Comment: Despite the fact that this child's defect measured 2.5 cm. in diameter a pressure gradient existed between left and right ventricles, indicating that the defect was less than 1 sq. cm. in area during ventricular systole. This discrepancy is explained by the position of the defect in the muscular septum permitting contraction of the defect during ventricular systole. In this instance, the ease of closure was facilitated by the fact that the defect lay far away from the conduction system and the possibility of complete heart block was made remote.

Unfortunately, serial electrocardiograms were available only over the last year of her life (Fig. 26). These tracings indicate persistent right ventricular hypertension and strain of the pressure overload type and right atrial hypertrophy as well. Evidence of left ventricular hypertrophy was present in the left precordial

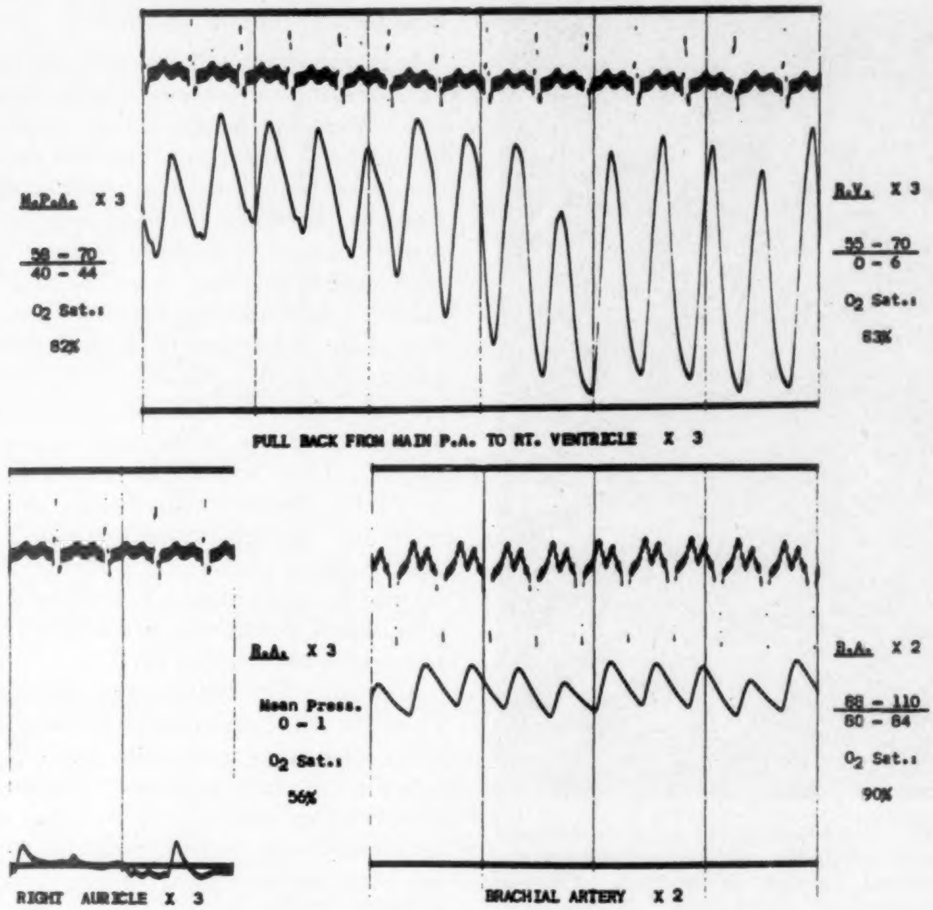


FIG. 24. Case 9. Medium-sized defect of muscular septum. Cardiac catheterization data.

leads where there were tall slow R waves and an upright coved T wave suggestive of left ventricular diastolic overload.

Evaluation of Clinical Course and Life History

We have reviewed the clinical syndromes associated with simple ventricular septal defects and cited illustrative case histories. The course followed by patients with ventricular septal defects is not static, but rather dynamic. Also, at a given stage in the clinical course of a patient the picture may resemble that seen in several different varieties of ventricular septal defects. Therefore, in order to understand the natural history of ventricular septal defects, to select patients who are suitable for surgical correction and, in addition, to determine the ideal time when surgical correction should be undertaken, much attention must be paid to the sequence of change. A full understanding of the course of events should help us predict the subsequent course which a patient will follow. This is obviously more difficult in early infancy since a pattern has just been established.

Certain general rules have proved of real value in assessing a patient. These might be expressed in the form of questions to be answered by the physician.

(1) *Is the patient's total cardiac output increased or decreased?* An increased output, when factors such as anemia are ruled out, indicates that blood is being tapped off the systemic circulation into the pulmonary vascular bed, and consequently, that pulmonary resistance is lower than systemic resistance. A high output can be produced only by means of an increased stroke volume and/or a more rapid pulse rate. If stroke volume is increased, chamber size and, therefore, heart size must also be increased. Thus, in general, the greater the output, the larger the heart. On the other hand, when a simple ventricular defect exists, a low cardiac output indicates that the shunt is small or that pulmonary vascular or right ventricular outflow obstruction is present. Total heart size is

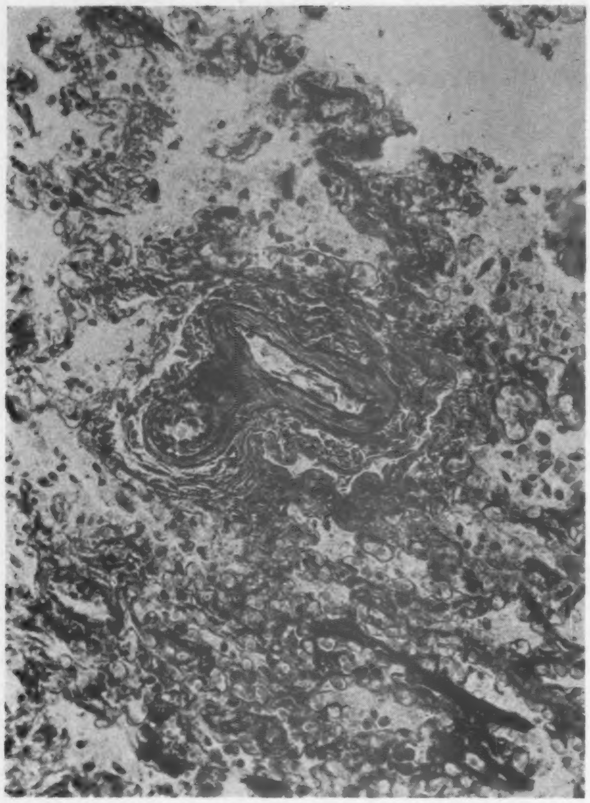


FIG. 25. Case 9. Photomicrograph of small muscular pulmonary artery. Note the marked medial hypertrophy and minimal intimal proliferation. Original magnification × 590.

little increased since stroke volume is low and the pressure demand on the right ventricle is only that which meets systemic resistance. The exception to this rule occurs when the picture is complicated by the presence of aortic or pulmonary valvular insufficiency.

(2) *Which ventricle is under the greatest stress?* When pulmonary resistance is low and pulmonary blood flow high, the left ventricle faces the greatest work load. When pulmonary resistance is high, and pulmonary blood flow low, the right ventricle is most severely stressed. Thus, the relative stress on the two ventricles can aid in determining the status of the pulmonary vascular bed and outflow tract of the right ventricle.

(3) *What evidence is there of a change in output or a change in ventricular stress, and in which direction is that change?* The proper answer to this question, we believe, is essential for proper management of the patient. Happily for the clinician, there are points in the history, physical examination and routine laboratory work which can prove of great aid in answering the question.

EVALUATION OF THE HISTORY

It is important to know at what time the first signs or symptoms relative to the heart appeared. Did congestive heart failure appear in early infancy? A history of repeated bouts of pneumonia or bronchitis associated with wheezing, rapid respirations, inability to take more than several ounces of formula without resting, and with failure to grow, suggests early congestive failure. It is also important to know how long this phase lasted and what constituted the next phase. Did the patient improve during the second year of life, become less dyspneic, fatigue less easily, grow and develop more normally? This sequence would suggest that either the patient with a large defect had entered the "golden period" in which pulmonary and systemic flows were relatively balanced, or that the patient had a medium-sized ventricular septal defect which became relatively less important as the child aged.

Cyanosis: The history of cyanosis is not enough in itself; it is important to know when the cyanosis first appeared, how serious it was and whether it improved or became worse. A history of cyanosis in the first few weeks of life in infants with large ventricular septal defects, or with medium-sized defects and congestive failure is not uncommon. This cyanosis is usually transient, seen only with severe stress, and improves with the passage of time. If it persists and becomes worse, it suggests either more cardiac failure or a rapid progression of pulmonary vascular disease. The occurrence of late cyanosis, appearing usually after the age of ten years, suggests a reversal of shunt due to either progressive pulmonary vascular disease or to significant outflow tract obstruction of the right ventricle.

EVALUATION OF PHYSICAL FINDINGS

The major points in the physical examination to be evaluated are evidence of failure, evidence of cyanosis, heart size and auscultatory findings.

Heart Failure: In early infancy failure does not manifest itself as it does in the adult. Rapid respirations are common. As a rule, the presence of a liver which has a firm edge, even though only slightly enlarged, indicates chronic passive congestion. Pitting edema is absent, but the skin of the extremities feels thick and wooden. The lungs, even in the presence of severe left heart failure, are surprisingly clear or else the findings suggest pneumonia. Cyanosis of the lips and nail beds should be searched for.

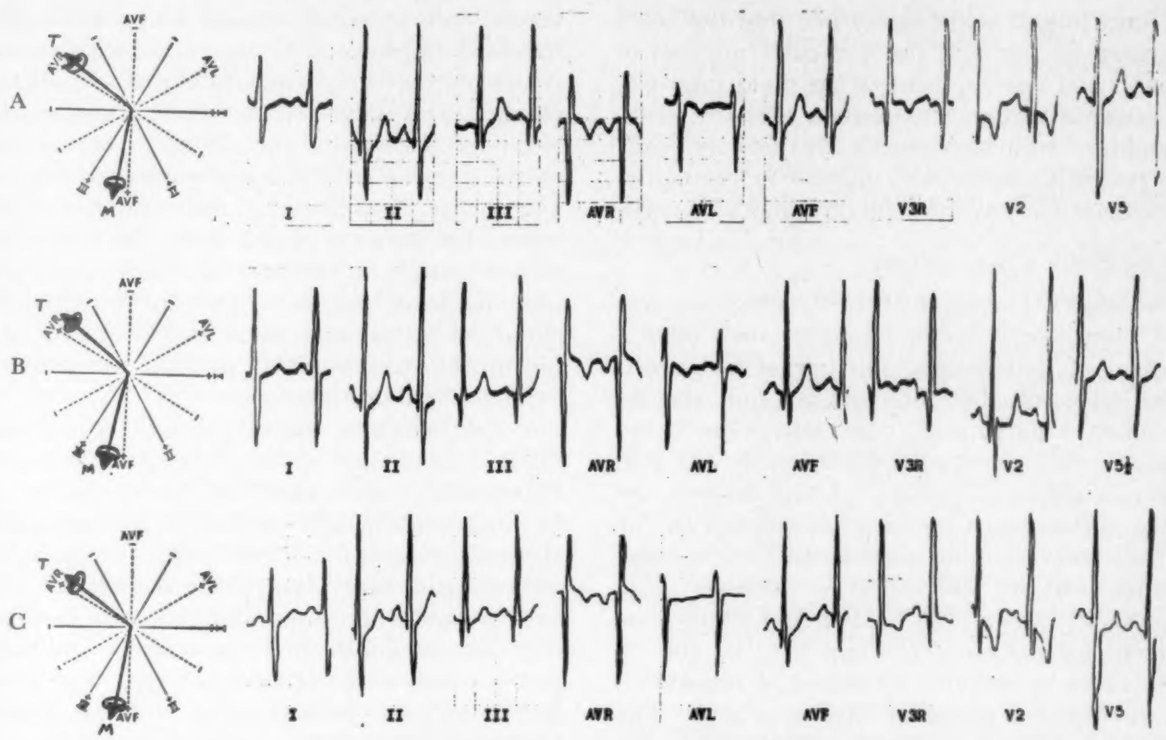


FIG. 26. Case 9. *Left*, electrocardiographic vectors. A, age eight years. B, age eight years. C, age eight years. In essence, these tracings indicate persistent right ventricular hypertrophy and strain, and right auricular hypertrophy without change over the period for which the tracings were available. *Right*, retouched serial electrocardiograms. A, age seven years, January 21, 1958. B, age eight years, July 9, 1958. C, age eight years, December 4, 1958.

Heart Size: A bulge of the precordium indicates right ventricular enlargement. An apical impulse displaced laterally and inferiorly suggests left ventricular enlargement. At times the difference between the amplitude of pulsations at the apex and those close to the sternum may afford an excellent means of determining which ventricle is under stress. Increased precordial activity suggests a high cardiac output. When severe pulmonary vascular disease is present, the precordium is usually quiet except at the base of the heart where a forceful second thrust is palpable.

Auscultatory Findings: Most ventricular septal defects are associated with a *systolic murmur*. One must assess the murmur position, its quality, duration and intensity. A murmur heard primarily at the base of the heart suggests right ventricular outflow tract obstruction. As a rule the murmur of a ventricular defect is heard lower over the sternum in the third and fourth left interspace. Large defects, either with or without high pulmonary blood flows, are associated with murmurs of low intensity, short duration and low pitch. Medium and small defects, because of the presence of a pressure gradient from left to right ventricle, are associated with thrill and a higher pitched, louder and longer systolic murmur which transmits better over the pulmonary parenchyma.

A *mid-diastolic rumble* heard at the apex is a common finding when pulmonary blood flow is increased. The etiology of this murmur is thought to be relative mitral stenosis due to a high venous return to the left atrium and normal mitral valve orifice. The presence of such a murmur, therefore, suggests high output and low pulmonary resistance. A *decrescendo diastolic murmur* along the left sternal border suggests pulmonary insufficiency most commonly found in patients with high pulmonary vascular resistance. A split pulmonary second sound is common in normal infants; however, if the intensity of the sound is increased, it suggests a high pulmonary resistance.

The importance of the physical examination is not limited to one examination. The sequence of changes is vital. We advise frequent examinations of patients with congenital heart disease, particularly during infancy when changes may be rapid and dramatic. Thus, in the patient in whom the systolic murmur becomes less intense, the mid-diastolic murmur disappears and the pulmonary second sound

becomes louder at the same time that the heart decreases in size and the over-all symptoms of growth and development of the child improve, progressive pulmonary vascular disease is developing. In infants especially, this may occur in a period of months and, unless seen frequently, the chance for corrective surgery may be missed.

LABORATORY EXAMINATIONS

Radiology: The value of chest roentgenograms and fluoroscopy lies first in that they offer a method of determining the size of the heart, vascularity of the lung fields and specific chamber enlargement. Secondly, an x-ray film affords a permanent record with which to evaluate sequential change. Unfortunately, the value of the record is somewhat reduced by the difficulty of obtaining good x-ray films in small infants, and by differences in technic. The vascularity of the lung fields is frequently misjudged, for apparent changes may be due to differences in technic, the phase of respiration or whether the patient is crying or not. The same is true to a lesser degree of the relative size of the heart. The position of the heart, however, is of value. In infants a heart that rests horizontally on the diaphragms indicates right ventricular enlargement. A heart that assumes a 45 degree angle, the apex extending down and out and perhaps not clearing the diaphragm on deep inspiration, suggests definite left ventricular enlargement. Except in small infants, deviation of the barium-filled esophagus is the best means of assessing left atrial enlargement.

Electrocardiogram: Of all the tools at our disposal, the electrocardiogram offers the most efficient simple method of assessing the patient. The electrocardiogram is a permanent record, and differences in technic are not so misleading. This is particularly true of the standard and augmented limb leads. A single record indicates which ventricle is under the greater stress, but does not portray what occurred before and hence what may be expected to happen in the future. Serial electrocardiograms afford the best method of evaluating the sequence of events. Among the illustrative case histories included in this discussion and all the patients with proved ventricular septal defects for whom serial electrocardiograms were available, the pattern of the electrocardiographic series clearly outlined the clinical course and final outcome.

In the case histories analyzed in this discussion, several terms are used to qualify the electrocardiographic tracings. The mean QRS vector and terminal vectors are used in the standard fashion. The terms "right and left ventricular activity" are used to denote patterns in the chest leads which indicate increased electrical activity of the ventricle not of the magnitude to imply hypertrophy or strain. The terms "hypertrophy and strain" are reserved for patterns which meet the usual accepted criteria. The terms "systolic and diastolic overload" are those used by the Mexican school of cardiology although we prefer the substitution of the terms "pressure and volume overload," respectively.

Vector analysis, including both the mean QRS and terminal vectors, in conjunction with evaluation of the precordial leads, appears to be the most objective method of analyzing the electrocardiographic record. By this method, patients with large ventricular defects fall into two groups; (1) those patients who develop high output failure in early infancy and then pass through a "golden period" due to progressive pulmonary vascular disease, initially show a pattern of left ventricular preponderance which shifts to a pattern of increasing right ventricular electrical activity and finally right ventricular preponderance; and (2) those in whom high output failure does not occur and who show a pattern of right ventricular preponderance which becomes more pronounced. Patients with large medium-sized defects initially demonstrate left ventricular preponderance which becomes either more left or reverses to right ventricular preponderance depending upon the response of the lungs and right ventricle. In patients with small medium-sized defects the pattern is initially left and almost invariably tends further to the left. In those patients with small ventricular defects, the pattern early in infancy may suggest abnormal left ventricular activity which becomes progressively more normal with the passage of time. The development of right ventricular outflow tract obstruction is reflected by evidence of increasing electrical activity of the right ventricle roughly proportional to the degree of obstruction.

In our experience progressive increase in right ventricular electrical activity constitutes a definite warning sign and means either progressive pulmonary vascular disease or outflow tract obstruction. The occurrence of this sequence makes mandatory early cardiac catheterization, and early surgical intervention if the obstruction is found distal to the right ventricle.

Cardiac Catheterization: Today, even with all the knowledge that can be gained by the use of readily available clinical and laboratory tools, we still lack sufficient "know-how" to judge these data accurately. Supportive evidence obtained from cardiac catheterization is essential to proper assessment. The details of cardiac catheterization are dealt with elsewhere. In this portion of the symposium it is important only to stress that catheterization can supplement clinical information with objective and quantitative data which are indispensible. First, the pressure of a ventricular septal defect can be established. Its functional size, position and role may be judged. The magnitude of stress placed on each side of the heart and on the lungs and the volume of shunt and degree of pulmonary vascular resistance may be assessed. The question of whether or not right ventricular outflow obstruction exists can be answered. Finally, serial catheterizations may help to quantitate the changes that take place, thereby increasing our understanding of the many possible syndromes associated with ventricular defects.

Conclusion

In this portion of the symposium we have discussed the anatomy, physiology and natural history of simple ventricular septal defect. Our understanding of this dynamic, progressively changing condition is not as yet complete. We need detailed serial studies on many patients starting in early infancy and carried through the operative correction of the defect. This should include repeated physical examination, serial x-rays and electrocardiograms and repeated catheterizations. The operative cardiac findings must be included as well as an assessment of the morphological pulmonary vascular changes. Only by such serial study may we arrive at the degree of understanding that will lead to the proper selection of patients for surgery and, more importantly, the ideal time for surgery.

References

1. Gould, S. E. Pathology of the Heart. Springfield, Ill., 1953. Charles C Thomas.
2. Keith, J. D., Rowe, R. and Vlad, P. Heart Disease in Infancy and Childhood. New York, 1958. Macmillan Co.
3. Ferencz, C. Atrio-ventricular defect of membranous septum: left ventricular-right atrial communication with malformed mitral valve simulating aortic stenosis. Report of a case. *Bull. Johns Hopkins Hosp.*, 100: 209, 1957.
4. Morris, E. W. I. The interventricular septum. *Thorax*, 12: 304, 1957.
5. Reemisma, K., Copenhaver, W. M. and Creech, O. The cardiac conduction system in congenital anomalies of the heart. Studies on its embryology, anatomy and function. *Surgery*, 44: 99, 1958.
6. Lev, M. The architecture of the conduction system in congenital heart disease. I. Common atrioventricular orifice. *Arch. Path.*, 65: 174, 1958.
7. Edwards, J. E. Defects of the ventricular septum. In: Pathology of the Heart, Chapt. 5, p. 288. Edited by Gould, S. E. Springfield, Ill., 1953. Charles C Thomas.
8. Dawes, G. S., Mott, J. C., Widdicomb, J. G. and Wyatt, D. G. Changes in the lungs of the newborn lamb. *Am. J. Physiol.*, 121: 141, 1953.
9. Dexter, L., Dow, J. W., Haynes, F. W., Whittenberger, J. L. and Ferris, B. G. Circulation in man at rest. Normal variations and the interrelations between increased pulmonary blood flow; elevated pulmonary arterial pressure and high pulmonary "capillary" pressures. *J. Clin. Invest.*, 29: 602, 1950.
10. Dawes, G. S., Mott, J. C. and Widdicomb, J. G. The patency of the ductus arteriosus in newborn lambs and its physiologic consequences. *Am. J. Physiol.*, 128: 361, 1955.
11. Dammann, J. F. and Ferencz, C. The significance of the pulmonary vascular bed in congenital heart disease. I. Normal lungs. II. Malformations of the heart in which there is pulmonary stenosis. *Am. Heart J.*, 52: 7, 1956.
12. Burton, A. C. Relation of structure to function of the tissues of the wall of blood vessels. *Physiol. Rev.*, 34: 619, 1954.
13. Patel, D. J. and Burton, A. C. Active constriction of small pulmonary arteries in rabbits. *Circulation Res.*, 5: 620, 1957.
14. Reynolds, S. R. The fetal and neonatal pulmonary vasculature in the guinea pig in relation to hemodynamic changes at birth. *Am. J. Anat.*, 98: 97, 1956.
15. Burton, A. C. On the physical equilibrium of small blood vessels. *Am. J. Physiol.*, 164: 319, 1951.
16. Dammann, J. F., Smith, R. T. and Muller, W. H. The experimental production of pulmonary vascular disease. *S. Forum*, 6: 155, 1955.
17. Dammann, J. F., Baker, J. P. and Muller, W. H. Pulmonary vascular changes induced by experimentally produced pulmonary arterial hypertension. *Surg., Gynec. & Obst.*, 150: 16, 1957.
18. Blank, R., Dammann, J. F. and Muller, W. H. Changes in pulmonary vascular lesions after restoring normal pulmonary artery pressure. *S. Forum*, 9: 356, 1958.
19. Dammann, J. F. The relationship of flow to pressure in various types of congenital heart disease, particularly those associated with pulmonary hypertension. In: Pulmonary Circulation. New York, 1959. Grune & Stratton, Inc.
20. Dammann, J. F. and Ferencz, C. The significance of the pulmonary vascular bed in congenital heart

disease. III. Defects between the ventricles or great vessels in which both increased pressure and blood flow may act upon the lungs and in which there is a common ejectile force. *Am. Heart J.*, 52: 210, 1956.
21. Wood, E. Hemodynamic alterations associated with septal defects and aortic-pulmonary communications. Presented at American Association for the Advancement of Science, Symposium on Congenital Heart Disease, December 1958.
22. Kirklin, J. Personal communication.
23. Wood, P. Pulmonary hypertension. *Mod. Concepts Cardiovas. Dis.*, 28: 513, 1959.
24. Sirak, H. D. and Hosier, D. M. Creation of a temporary artificial ductus for the surgical correction of ventricular septal defects associated with severe pulmonary hypertension. *J. Thoracic Surg.*, 37: 1, 1959.
25. Gerbode, F. L. Discussion of paper by Lillehei, E. W. *J. Thoracic Surg.*, 37: 270, 1959.
26. Bailey, C. P. Discussion of paper by Sirak, H. D. *J. Thoracic Surg.*, 37: 270, 1959.

Some Physiologic and Hemodynamic Observations in Ventricular Septal Defect*

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HEMODYNAMIC findings in ventricular septal defect are the consequences of an abnormal communication between two independent pressure systems. The sequence of events in this disease depends mainly on the size of the septal defect and the existing pressures in the pulmonary and systemic circulation.

Important contributions in the past few years[1–10] have clarified some of its many aspects. Contrary to classic concepts, severe forms of ventricular septal defect leading to early invalidism and death are relatively frequent[6–8] and survival is relatively rare beyond the age of forty-five years apart from the tendency for ventricular septal defect to be complicated by bacterial endocarditis.

MATERIAL AND METHODS

The observations presented are based on data in eighty-two patients catheterized in the Fundacíon Castellanos and in the Instituto de Cirugia Cardiovascular. Data on an additional eighty-five patients in whom diagnosis rested only on clinical observation and angiocardiography were not included. Catheterization was performed in the accepted manner. The Fick principle was applied in all cases to determine cardiac output. The formulas employed for the determination of shunts are those of Handelsman and co-workers.[10] Pulmonary arteriolar resistance and total pulmonary resistance were calculated according to methods of Gorlin et al.[11] In small children whose cooperation could not be obtained a light Pentothal® anesthesia was used during catheterization. In the remaining patients, premedication with Nembutal,® 0.1 gm., was employed. Since anesthesia is known to produce slight unsaturation of arterial oxygen, we considered 90 per cent saturation the limit of normal.

In all but one patient, the diagnosis of ventricular septal defect was established when a gradient of 1 vol. per cent or more was found between the mean of various right atrial samples and that obtained from the right ventricle. In one patient, a rise of 0.75 vol. per cent in the right ventricle is considered significant because of characteristic clinical and angiocardiographic findings.

Included in this study are sixty-four patients with a drop in systolic pressure between the right ventricle and the pulmonary artery. The magnitude of the systolic gradient was always less than 25 mm. Hg.

Although the determination of pressures in the pulmonary circulation is subject to small errors if the manometer system is adequate, the application of the Fick principle and consequently the determination of shunts and pulmonary resistances may be subject to considerable error.[12]

CLASSIFICATION

We classified our patients according to the existing systolic pressure in the right ventricle (Table I). This classification is essentially the same as that of Selzer, based on anatomic findings,[1] if it is assumed that the degree of left-to-right shunt as determined during cardiac catheterization represents the size of the defect. Right ventricular systolic pressure rather than pulmonary artery pressure was used because of the existing gradient between the right ventricle and the pulmonary artery, frequently found in ventricular septal defect.

This classification gives a panoramic view of the relative incidence of the various forms and degrees of severity in this cardiac malformation. Ventricular septal defect with hypertension is relatively common,[9] representing more than half of the cases in this study.

In Table I, group IIB corresponds to the so-called Eisenmenger complex. Modern views consider the Eisenmenger complex a severe form of ventricular septal defect. Hemodynamic studies[4,7] as well as anatomic observations[2,4] indicate that the presence of central cyanosis, i.e., right-to-left shunt, in the Eisenmenger

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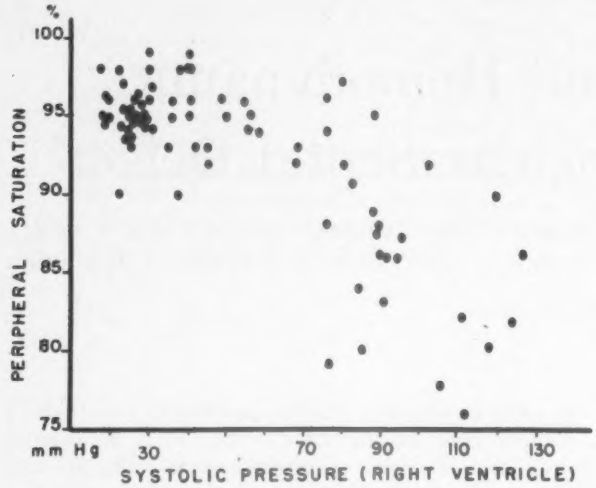

FIG. 1. Relationship between right systolic ventricular pressure and peripheral saturation. Peripheral saturation decreases below 90 per cent when right ventricular systolic pressures are above 70 mm. Hg.

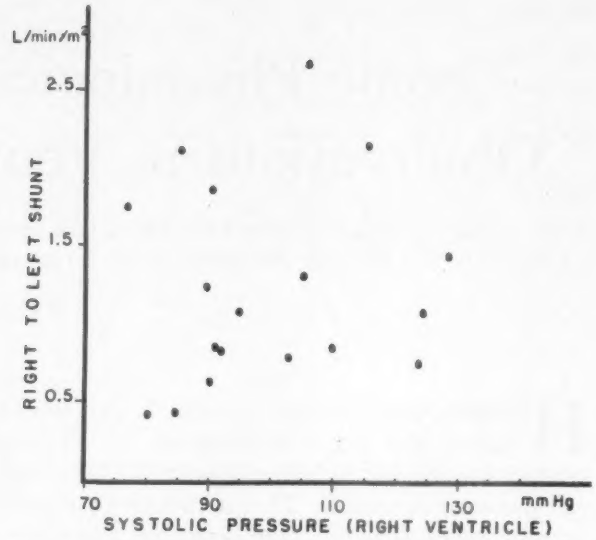

FIG. 2. Right-to-left shunt increases in a linear fashion with increases in right ventricular systolic pressure.

complex is not related to an overriding aorta but to the degree of pulmonary hypertension and elevation of pulmonary resistance. The aorta, because of its anatomic location, unless it arises entirely from the right ventricle, even if it is overriding, can receive little, if any, blood from the right ventricle, as long as right ventricular pressure is normal or slightly elevated and well below the level of left ventricular pressure.

The separation of patients with pulmonary hypertension and left-to-right shunt only (Table I, group IIA) from those with an associated right-to-left shunt (Table I, group IIB) is difficult. In many patients who show pulmonary hypertension and left-to-right shunt

TABLE I

Classification of Cases According to Right Ventricle Pressures

Right Ventricular Systolic Pressure	No. of Patients
I. Normal right ventricular systolic pressure (below 35 mm. Hg)	35*
A. With small left-to-right shunt (less than 3 L./min./M²)	22
B. With large left-to-right shunt (more than 3 L./min./M²)	7
II. Abnormally elevated right ventricular systolic pressure (above 35 mm. Hg)	47*
A. With left-to-right shunt only	27
B. With right-to-left shunt in addition	16

* In six patients belonging to group I and in four belonging to group II cardiac output was not obtained.

during catheterization a right-to-left shunt develops during minor respiratory infections or during exercise.

RESULTS

The results of cardiac catheterization are summarized in Table II, in which patients are arranged according to age in years at the time they were studied.

Pressures: In five patients with hypertension, the catheter was introduced from the right ventricle into the aorta. Thirty-seven patients had normal pressures in the pulmonary circulation and forty-five had various degrees of pulmonary hypertension. Right atrial mean pressure was normal in all but three patients, and no significant difference was found between mean atrial pressure in patients with pulmonary hypertension, and those with normal pressure. The atrial "a" wave was significantly higher in the patients with pulmonary hypertension. Mean pulmonary "capillary" pressure was normal in all patients. In the patients with hypertension mean pulmonary "capillary" pressure was significantly higher than in normotensive patients.

A drop in systolic pressure was found between the right ventricle and the pulmonary artery in sixty-four patients which ranged from 1 to 25 mm. Hg. This systolic gradient was more than 5 mm. Hg in thirty-one patients (38 per cent).

Oxygen Content: An increase in oxygen content of the mixed venous blood from the right atrium to the right ventricle occurred in all

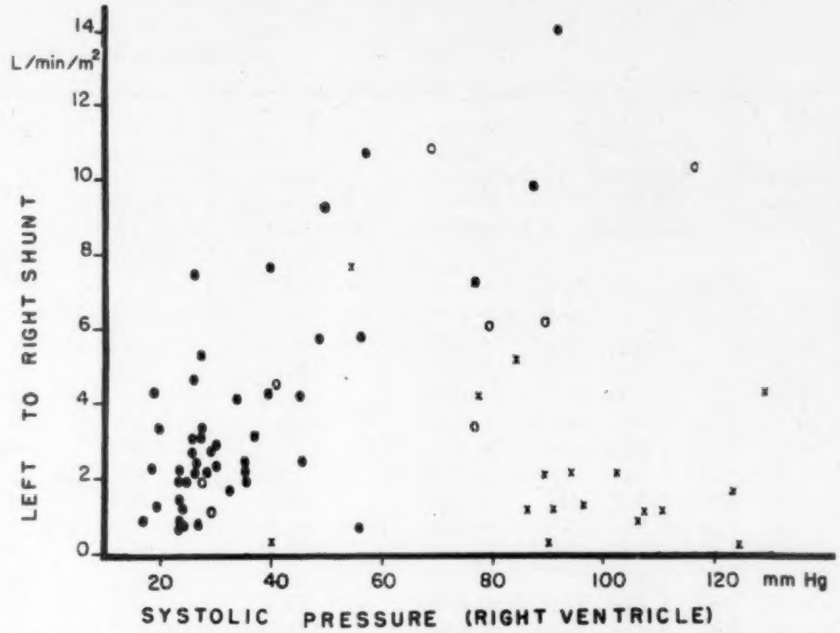

FIG. 3. Correlation of the left-to-right shunt with the right ventricular systolic pressure. Black dots represent normal pulmonary resistance (less than 300 dynes sec. cm.$^{-5}$). Open dots represent moderately elevated pulmonary resistances (between 301 and 500 dynes sec. cm.$^{-5}$). X represents pulmonary resistances over 501 dynes sec. cm.$^{-5}$ Increases in right ventricular systolic pressure between 35 and 60 mm. Hg are due mainly to increases in right ventricular output. Right ventricular systolic pressures above 80 mm. Hg are always associated with abnormally high pulmonary resistances.

cases. The highest oxygen content was found in the right ventricular inflow tract in fifty patients, in the right ventricular outflow tract in sixteen patients and in the pulmonary artery in sixteen patients. In this last group, aortography was performed in three patients to rule out the possibility of a persistent ductus arteriosus. In the remaining patients of this group, a diagnosis of isolated ventricular septal defect was established by angiocardiography and characteristic clinical findings. The magnitude of the left-to-right shunt in patients whose rise in oxygen content is found in the pulmonary artery and not at the level of the ventricle is significantly less than those whose oxygen gradient is found at the ventricular inflow or outflow tract.

Right-to-Left Shunt: In sixteen patients a right-to-left shunt was present in addition to the left-to-right-shunt. The presence of a right-to-left shunt was established when peripheral artery saturation was less than 90 per cent. All patients with right-to-left shunt had moderate to marked pulmonary hypertension (Figs. 1 and 2).

Pulmonary Resistance: Total pulmonary resistance was normal in twenty-one patients (below 300 dynes sec. cm.$^{-5}$), moderately increased in seventeen patients (between 301 and 500 dynes sec. cm.$^{-5}$), and markedly elevated in thirty-four patients (over 501 dynes sec. cm.$^{-5}$). Since pulmonary "capillary" pressures were normal in all patients, this increase in total pulmonary resistance was due to an increase in pulmonary arteriolar resistance. In ten patients oxygen consumption was not available, and cardiac flow and resistances were not obtained.

COMMENTS

The existing pressure in the right ventricle and pulmonary artery in ventricular septal defect depends on both the right ventricular output, i.e., magnitude of the left-to-right shunt, and the level of the pulmonary resistance. Figure 3 shows the relation of these factors to right ventricular systolic pressure. Increases in right ventricular systolic pressure in the 35 to 80 mm. Hg range are mainly due to increases in output determined by the left-to-right shunt. Pulmonary resistance remains normal. Increases in right ventricular systolic pressure above 90 mm. Hg are always associated with an abnormally elevated pulmonary resistance.

TABLE

Hemodynamic Findings in Eighty-Two

Case No.	Age (yr.)	Surface Area (M^2)	Systemic Flow (cc./min.)	Pulmonary Flow (cc./min.)	Oxygen Saturation (%)	Right Atrial, Mean	Right Ventricular	
							Systolic/ Diastolic	Mean
1	0.3	0.27	1,076	2,382	88	−0.2	84/6	30
2	0.4	0.33	2,530	3,380	93	1.0	45/6	25
3	0.5	0.32	1,120	2,540	95	1.5	40/5	27
4	0.6	0.36	1,820	5,020	80	1.7	117/17	60
5	0.6	0.26	980	2,964	99	3.2	41/5	22
6	0.7	0.35	1,445	2,112	95	3.1	28/5	16
7	1	0.40	1,343	2,593	90	0.5	37/4	18
8	1.7	0.47	2,846	6,453	96	3.2	54/7	28
9	2	0.54	1,845	2,490	95	0.8	18/1	10
10	2	0.47	1,355	1,912	99	0.6	30/2	11
11	2	0.46	1,840	4,410	94	5.1	56/4	30
12	2	0.62	3,484	9,930	94	1.7	58/4	30
13	2	0.44	1,560	7,554	86	−1.6	93/8	46
14	2.5	0.60	1,722	4,232	92	4.1	46/5	23
15	3	0.75	2,350	3,262	95	2.5	24/4	11
16	3	0.48	1,850	5,440	95	1.3	25/2	13
17	3	0.62	2,800	4,200	96	0.5	35/1	19
18	3	0.62	2,550	3,750	94	3.2	24/8	13
19	3	0.57	1,790	4,750	96	1.3	26/0	16
20	3	0.32	...	...	97	4.7	80/4	40
21	3	0.50	4,028	6,238	86	4.6	89/7	41
22	3	...	3,780	5,240	89	4.8	88/5	47
23	3	0.54	...	...	65	6.0	88/4	35
24	3	0.60	3,300	2,740	79	2.6	85/17	50
25	3	0.67	2,420	3,930	95	−0.2	23/1	9
26	4	0.64	2,730	5,500	96	0.5	19/2	9
27	4	0.73	2,420	3,875	98	−2.4	23/2	10
28	4	0.62	2,600	4,715	96	−0.8	19/0	7
29	4	0.68	2,500	29,90	90	2.6	23/4	10
30	4	0.62	2,305	4,428	96	0.4	76/5	43
31	4	0.60	1,850	1,772	88	2.8	89/6	42
32	4	0.71	3,951	4,516	89	4.4	88/8	38
33	4	0.56	1,655	4,210	96	0.2	42/3	18
34	4.5	0.64	2,800	9,800	93	0.4	69/7	34
35	5	0.70	1,290	2,150	98	−0.6	17/1	11
36	5	0.76	2,183	3,045	95	3.8	24/3	13
37	5	0.65	3,355	5,370	93	0.5	26/4	17
38	5	0.72	3,954	2,586	95	2.4	35/4	18
39	5	0.63	3,078	6,716	96	4.1	49/8	29
40	5	0.75	2,540	7,999	94	4.0	77/6	37
41	5	0.66	3,780	5,420	79	5.8	77/6	41
42	5	0.74	2,734	3,540	87	−1.1	95/2	48
43	5.5	0.82	2,820	5,380	95	0.6	26/6	16
44	6	0.75	...	...	92	4.4	68/6	34
45	6	0.85	2,570	3,855	93	6.5	23/6	11
46	6	0.80	2,510	4,652	93	1.0	25/1	11
47	6	0.72	...	...	94	2.2	24/4	11
48	7	0.82	2,176	4,995	95	1.2	26/6	16
49	7	0.95	3,620	6,270	94	−0.7	28/7	17
50	7	0.92	1,895	2,270	98	4.0	40/4	20
51	7	0.83	2,860	4,870	93	1.3	26/4	12
52	7	0.82	2,480	4,880	95	4.0	31/4	17

NOTE: Mean right atrial and "capillary" pressures and measurements of ventricular work are rounded off to the

II

Patients with Ventricular Septal Defect

Pressures (mm. Hg)					Pulmonary Resistance (dynes sec.cm.$^{-5}$)		Ventricular Work (Kg.M./min.)	
Pulmonary Artery		Pulmonary "Capillary" (Mean)	Systemic					
Systolic/Diastolic	Mean		Systolic/Diastolic	Mean	Total	Arteriolar	Right	Left
80/36	59	...	86/50	64	1,970	...	2.0	2.1
40/12	29	...	68/39	57	687	...	1.6	2.4
26/9	22	9.3	96/65	85	706	415	0.8	2.7
104/56	84	4.2	93/33	62	1,290	1,265	2.5	2.5
35/14	25	5.4	...	...	669	340	0.9	...
28/14	25	19.8	106/53	76	952	228	0.6	2.5
28/11	20	10.0	73/38	54	502	298	0.7	1.1
57/21	42	14.0	95/49	70	522	351	3.4	4.4
17/5	10	3.4	105/80	90	233	223	0.3	2.9
26/6	16	4.7	...	...	590	478	0.4	...
56/21	40	18.2	131/81	102	725	395	2.4	6.1
65/18	49	16.8	83/47	65	389	255	6.3	8.8
86/45	73	5.2	82/43	64	669	613	7.8	6.0
42/13	30	8.2	91/55	72	584	416	1.5	3.7
22/4	13	7.9	99/62	77	328	136	0.4	3.2
19/8	16	5.2	102/56	83	228	150	1.1	5.8
27/6	16	3.0	112/59	81	302	245	1.5	7.3
22/10	16	9.6	113/69	95	342	138	0.7	4.6
24/8	22	10.7	115/66	100	362	180	1.3	6.5
65/23	46	11.3	117/67	78	...	...	...	...
86/22	55	8.5	103/49	77	703	598	4.9	6.1
88/42	62	18.7	113/63	84	945	655	...	...
...	...	...	88/53	64	...	...	...	...
80/41	72	22.9	93/58	69	2,100	1,430	3.1	2.3
22/8	16	8.1	108/67	76	335	170	0.6	3.8
16/4	12	5.1	81/44	62	181	107	0.9	4.3
15/7	12	3.8	106/70	87	247	165	0.8	2.7
14/1	8	0.7	117/73	90	127	116	1.1	6.1
20/7	12	...	89/53	70	320	...	0.4	2.2
62/18	44	11.7	124/101	109	801	589	4.0	6.5
91/44	69	10.3	87/57	76	3,112	2,648	1.8	1.7
93/46	71	11.4	96/67	82	1,257	1,057	4.9	14.3
32/10	24	10.5	110/75	90	456	256	1.4	4.9
80/51	71	15.1	89/54	72	578	454	9.5	13.9
15/3	11	2.4	112/80	99	401	103	0.3	2.8
20/9	14	7.4	...	...	361	167	0.4	...
20/7	17	...	75/39	59	247	...	1.2	4.0
30/13	22	6.5	113/67	91	338	240	1.4	6.0
48/16	35	8.7	100/59	76	421	317	2.9	5.7
58/21	40	16.9	88/31	62	402	232	4.0	7.3
80/40	60	6.0	82/55	68	996	907	4.6	4.6
88/47	74	3.3	102/66	84	1,428	1,357	4.4	4.0
22/10	18	8.6	88/58	77	265	136	1.3	2.8
43/16	29	6.6	116/77	87	687	...	1.6	2.1
17/8	11	6.5	99/61	81	220	84	0.4	3.2
19/2	13	8.1	120/55	89	279	140	0.7	5.0
19/7	14	7.6	112/67	89	...	...	...	...
27/10	18	7.0	119/68	94	295	183	1.2	6.0
25/11	19	7.7	140/90	115	238	139	2.4	6.8
30/10	19	5.4	99/76	89	672	492	0.5	2.6
23/15	22	13.6	153/108	129	356	133	1.9	3.6
30/12	22	7.2	116/82	98	357	238	1.1	3.5

nearest tenth. Right ventricular, pulmonary artery and systemic pressures are expressed in the nearest whole number.

TABLE II

Case No.	Age (yr.)	Surface Area (M^2)	Systemic Flow (cc./min.)	Pulmonary Flow (cc./min.)	Oxygen Saturation (%)	Right Atrial, Mean	Right Ventricular	
							Systolic/Diastolic	Mean
53	7	0.66	2,235	6,078	92	5.5	80/11	75
54	7	0.85	4,420	4,060	78	3.3	105/6	61
55	8	0.91	2,790	4,950	98	2.6	30/7	15
56	8	0.85	4,868	5,346	95	4.5	50/3	22
57	8.7	0.87	...	...	96	6.4	29/6	19
58	9	1.10	...	...	98	4.8	37/2	16
59	9	1.18	6,010	10,860	97	5.2	35/0	15
60	9	0.88	4,810	7,400	86	−1.6	128/7	82
61	10	0.93	...	...	95	1.5	18/2	7
62	10	0.96	3,460	5,580	94	4.4	25/4	10
63	11	0.83	4,750	5,790	92	5.4	103/3	43
64	11	0.98	2,860	3,100	83	1.8	110/7	50
65	11	0.98	5,123	4,400	83	2.4	92/13	52
66	12	...	4,780	5,794	93	−0.1	42/4	19
67	13	1.15	...	...	98	7.0	41/13	23
68	13	1.12	4,773	13,480	95	1.5	76/7	45
69	15	1.55	4,930	6,340	97	5.9	23/6	17
70	15	1.45	...	...	88	4.1	73/6	41
71	16	1.42	5,710	3,886	86	2.7	95/13	46
72	18	1.38	3,325	9,750	95	1.8	25/4	12
73	19	1.42	5,790	9,064	94	5.9	19/6	10
74	21	1.81	6,190	7,780	89	8.5	123/18	54
75	23	1.34	3,580	6,450	93	...	35/5	13
76	26	1.42	3,680	2,320	82	7.0	124/15	56
77	27	1.40	4,610	5,510	96	1.1	20/4	10
78	29	1.33	6,750	19,250	95	1.3	50/5	30
79	30	1.49	6,430	4,250	75	8.0	107/10	55
80	33	1.70	4,560	7,430	97	5.0	32/1	10
81	35	1.48	6,440	10,040	95	−0.3	28/2	14
82	60	1.00	...	...	...	...	25/8	13

Pulmonary hypertension associated with increased pulmonary resistance may or may not be completely reversible; however, hypertension due to increased right ventricular output is reversible when the left-to-right shunt is suppressed.

Systolic Pressure Gradient Between Right Ventricle and Pulmonary Artery: An interesting point is the drop of systolic pressure between the right ventricle and the pulmonary artery frequently observed in ventricular septal defect.[7,9–11] Brotmacher and Campbell[13] discussed this finding in a study of ventricular septal defect with associated pulmonary stenosis.

Barrat-Boyes and Wood[14] found systolic gradients of 5 mm. Hg in a group of normal subjects. Personal observations [15] of sixty-nine patients with mitral stenosis where pulmonary stenosis could be safely ruled out and of fifty-nine patients with interatrial septal defects without pulmonary stenosis have shown systolic gradients between the right ventricle and the pulmonary artery varying from 1 to 9 mm. Hg and from 1 to 15 mm. Hg, respectively. Figure 4 shows the relationship of the systolic gradient to the systolic ventricular pressure and the magnitude of shunt. The largest mean gradient lies in the systolic pressure group of 50 to 70 mm. Hg, and corresponds to the largest mean left-to-right shunt. It decreases strikingly above and below this range. The literature reviewed shows that largest gradients occur when the range of ventricular systolic pressures is between 45 and 75 mm. Hg.[9,10,13,17,18]

We believe these patients represent cases of ventricular septal defect without anatomic pulmonary stenosis. Two patients reported here (Cases 5 and 20) who came to autopsy had

(*Continued*)

Pressures (mm. Hg)					Pulmonary Resistance (dynes sec. cm.$^{-5}$)		Ventricular Work (Kg.M./min.)	
Pulmonary Artery		Pulmonary "Capillary" (Mean)	Systemic					
Systolic/ Diastolic	Mean		Systolic/ Diastolic	Mean	Total	Arteriolar	Right	Left
65/36	55	28.2	101/77	92	721	345	4.5	5.3
99/62	81	7.7	105/58	83	1,585	1,435	4.7	4.3
23/7	15	7.3	124/68	92	243	124	0.8	5.9
30/12	20	7.7	104/75	92	296	180	1.1	6.1
29/16	24	11.6	118/80	99	...	...	...	...
25/8	16	10.1	117/63	88	...	...	...	...
28/9	19	8.7	153/88	116	154	84	4.8	12.5
133/81	105	8.5	117/76	100	1,137	1,042	12.5	9.5
18/7	13	10.5	106/67	87	...	...	...	...
23/6	14	10.5	114/61	95	202	50	0.7	4.2
106/49	73	7.1	108/62	83	1,065	966	5.6	6.9
106/62	85	4.6	120/76	96	2,181	2,073	4.4	3.9
120/50	95	6.2	96/77	83	1,723	1,608	5.8	5.5
38/15	24	8.8	143/78	106	342	220	1.2	7.9
38/14	19	12.0	120/75	84	...	...	...	...
65/22	46	9.0	104/84	98	255	209	10.1	17.9
19/9	15	8.9	128/76	96	189	76	0.8	7.9
65/37	54	13.7	100/66	84	...	...	...	...
87/44	66	1.1	104/72	88	1,353	1,341	4.9	6.4
23/5	16	4.7	146/86	112	590	478	0.4	...
18/9	14	14.8	113/77	95	120	32	1.0	9.8
118/50	92	19.0	120/65	90	985	790	7.8	9.5
25/10	15	9.2	121/74	95	186	718	0.9	5.8
121/69	86	5.5	105/68	82	2,970	2,790	2.8	4.3
14/8	9	...	113/84	109	133	...	0.6	7.8
50/14	27	9.8	112/68	84	111	73	6.6	7.2
108/62	78	...	107/66	77	1,460	...	4.3	6.6
29/8	18	12.3	150/86	103	314	99	0.9	10.4
15/3	9	8.0	128/68	94	748	...	3.1	12.1
25/13	18	15.2	164/89	136	...	...	...	...

respectively 5 and 16 mm. Hg gradients and no anatomic stenosis could be found.

The patients in this group with a ventricular systolic gradient cannot be considered to have mild forms of tetralogy of Fallot, as those reported by McCord and co-workers (types III and IV), because no evidence of infundibular stenosis could be found.[19] However, some of the cases reported as types III and IV of tetralogy of Fallot by these authors could be considered as isolated ventricular septal defect with marked hypertrophy of the crista ventricularis leading to infundibular stenosis.[20]

The cause of the systolic gradient in ventricular septal defect is not entirely clear. It may be due in part to the functional effect of a large right ventricular systolic volume with increased velocity of flow passing from a dilated right ventricle through a normal pulmonary artery ring. The coincidence of the largest shunt with the greatest gradient is consistent with this interpretation.

Rise in Oxygen Content at Pulmonary Artery Level: In five patients the rise in oxygen content was present at the pulmonary artery while the ventricular sample had no significant increase in oxygen. The calculation of the left-to-right shunt in these patients was significantly less than those in whom the oxygen content was significantly higher at the level of the right ventricle. This is probably due to incomplete mixture of the shunted blood at the ventricular level and has been reported previously.[7] Clinical findings are usually characteristic and permit diagnosis to be made in the absence of aortography, especially if normal ventricular pressures are found.

Size of Shunt and Hemodynamic Findings:

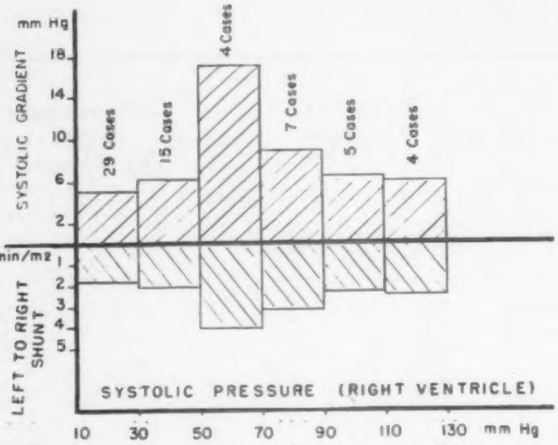

Fig. 4. The systolic gradient between the right ventricle and the pulmonary artery trunk has been placed above the line, the left-to-right shunt below the line. Each block represents the mean of cases occurring in the corresponding range of ventricular systolic pressures. The largest gradients correspond with the largest left-to-right shunts and occur between 50 and 90 mm. Hg systolic pressure.

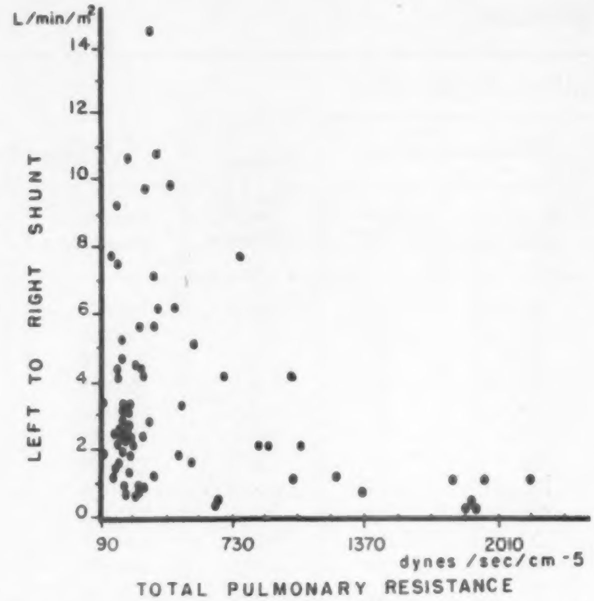

Fig. 5. Correlation between left-to-right shunt and total pulmonary resistance. Left-to-right shunt decreases sharply above 500 dynes sec. cm.$^{-5}$

Analysis of the data presented in Table II is in agreement with the suggestion that the size of the ventricular septal defect is the principal factor in determining the hemodynamic changes.[2] Patients grouped as IA and IB in Table I represent smaller defects capable of maintaining a differential pressure between the left and right ventricles. The magnitude of the left-to-right shunt is a function of the size of the defect and the pressure gradient between the two ventricles. Pulmonary resistance is normal in this group.

Patients in group II have larger defects. The pulmonary hypertension is due to the increased right ventricular output, increased pulmonary resistance or both. In this group left ventricular pressures are freely transmitted to the right ventricle and the magnitude of the left-to-right shunt is determined by the pulmonary resistance. Figure 5 shows the effect of increasing pulmonary resistance on the degree of left-to-right shunt. It is apparent that higher pulmonary resistances are associated with a sharp reduction of the left-to-right shunt.

Right-to-Left Shunt: As the pulmonary resistance increases, the level of the right ventricular systolic pressure approaches that of the existing pressure in the left ventricle and a right-to-left shunt occurs. This happens whether the aorta is transposed or normally placed. Figures 1 and 2 illustrate the relations between the right-to-left shunt and ventricular systolic pressure, and the degree of peripheral unsaturation and right ventricular systolic pressure. Both show that appearance of the right-to-left shunt occurs at a high level of right ventricular systolic pressure.

Causes of Increased Pulmonary Resistance: The mechanism that determines the changes in pulmonary resistance is unknown. Age has no relation to the level of pulmonary resistance. The degree of left-to-right shunt is apparently not the main factor in the production of changes of pulmonary resistance. Blount and coworkers[18] have suggested that the force of ejection into the pulmonary vascular tree may play a role in the arteriolar changes leading to an increase in pulmonary resistance. The group of patients with hypertension and elevated pulmonary resistance (Cases 1, 2 and 4) in infants less than one year old may represent a congenital defect of the pulmonary vascular tree. Teleologically this may be a protective mechanism for survival.[4] During the first months of life, the increased pulmonary resistance normally present during fetal life[16] gradually drops, and the pulmonary circulation progressively develops into a low pressure system. In a large septal defect with equalized pressures in both ventricles, the pulmonary flow and consequently the left-to-right shunt, is determined by the pulmonary resistance. If pulmonary resistance is low, the increased left-to-right shunt occurs at the expense of the

systemic flow, which may be inadequate to maintain life.

Serial observations of thirty patients with ventricular septal defect during eight years[21] have shown that pulmonary resistance and pressure fell from abnormally high to near normal levels in five patients. Twelve patients had no significant change, three patients with initially normal pressures and pulmonary resistances had significant increases in both, and the remaining ten patients, who initially had pulmonary hypertension and elevated pulmonary resistance, had further increases in both. According to these authors, pulmonary resistances tend to follow a progressive course after varying intervals of "latency." The mechanism by which these changes occur remains obscure.

Summary

The hemodynamic data of eighty-two patients with ventricular septal defect are presented.

A drop in systolic pressure between the right ventricle and pulmonary artery trunk was present in sixty-four patients. The largest gradient found was 25 mm. Hg. We believe this gradient does not represent an associated pulmonary stenosis but is due rather to functional effects. Analysis of the hemodymanic data suggests that the size of the ventricular septal defect is the principal factor determining the various changes. In smaller septal defects, the magnitude of the left-to-right shunt is a function of the size of the hole. Pulmonary resistance determines the magnitude of the left-to-right shunt in larger defects. The presence or absence of a right-to-left shunt depends on right ventricular pressure. The mechanism by which changes in the pulmonary resistance occur remains unknown.

References

1. Selzer, A. Defects of the cardiac septum. *J. A. M. A.*, 154: 129, 1954.
2. Selzer, A. and Laquer, G. L., The Eisenmenger complex and its relation to the uncomplicated defect in the ventricular septum. *Arch. Int. Med.*, 87: 218, 1951.
3. Selzer, A. Defect of the ventricular septum. *Arch. Int. Med.*, 84: 798, 1949.
4. Edwards, J. E., Functional pathology of the pulmonary vascular tree in congenital heart disease. *Circulation*, 15: 164, 1957.
5. Brostoff, P. and Rodbard, S. Hydrodynamics in ventricular septal defects. *Am. Heart J.*, 51: 325, 1956.
6. Maxwell, G. M., Rowe, G. C. and Crumpton, C. W., Clinical and hemodynamic study of ventricular septal defect in infants. *Arch. Dis. Child.*, 33: 67, 1958.
7. Brotmacher, L. and Campbell, M., The natural history of ventricular septal defect. *Brit. Heart J.*, 20: 97, 1958.
8. Marquis, R. M. Ventricular septal defect in early childhood. *Brit. Heart J.*, 12: 265, 1950.
9. Joly, F., Carlotti, J. and Sicot, J. R. Les communications interventriculaires. *Arch. mal. coeur*, 44: 602, 1951.
10. Handelsman, J. C., Bing, R. J., Campbell, J. A. and Griswold, H. E. Physiological studies in congenital heart disease. v. The circulation in patients with isolated septal defects. *Bull. Johns Hopkins Hosp.*, 82: 615, 1948.
11. Gorlin, R., Haynes, F. W., Sawyer, C. G., Dow, J. W. and Dexter, L. Studies of the circulatory dynamics in mitral stenosis. II. *Am. Heart J.*, 41: 30, 1951.
12. Visscher, M. B. and Johnson, J. A., The Fick principle: analysis of potential errors in its conventional application. *J. Appl. Physiol.*, 5: 635, 1953.
13. Brotmacher, L. and Campbell, M. Ventricular septal defect with pulmonary stenosis. *Brit. Heart J.*, 20: 379, 1958.
14. Barrat-Boyes, B. C. and Wood, E. H. cited by Callahan, J. A., Brandenburg, R. O. and Swan, H. J. C. Pulmonary stenosis and ventricular septal defect with arteriovenous shunts. *Circulation*, 12: 994, 1955.
15. García, O. and Barrera, F. Personal observations.
16. Civin, W. H. and Edwards, J. E. Post-natal structural changes in the intrapulmonary arteries and arterioles. *Arch. Path.*, 51: 192, 1951.
17. Lequime, J., Courtoy, P., Denolin, H. and Kenis, J. La dinamique circulatiore des communications interventriculaires isolées. *Cardiologia*, 21: 529, 1952.
18. Blount, S. C., Mueller, H. and McCord, M. C. Ventricular septal defect. *Am. Heart J.*, 18: 871, 1955.
19. McCord, M. C., van Eek, J. and Blount, S. C. Tetralogy of Fallot. Clinical and hemodynamic spectrum of combined pulmonary stenosis and ventricular septal defect. *Circulation*, 16: 736 1957.
20. Gasul, B. M., Dillon, R. S., Vrla, V. and Hait, G. Interventricular septal defect. The natural transformation into those with infundibular stenosis or into the cyanotic or non-cyanotic type of tetralogy of Fallot. *J. A. M. A.*, 164: 847, 1957.
21. Adams, P., Anderson, R. C., Allen, P. and Lillehei, C. W. Physiologic changes with age in ventricular septal defect. *Circulation*, 16: 857, 1957.

Isolated Ventricular Septal Defects

An Anatomic-Hemodynamic Correlation*

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ANATOMICALLY, isolated interventricular septal defects vary in location, size, shape and character and in association with pulmonary vascular abnormalities. Embryologically, these defects are due to arrest in the development of one or several of the elements which participate in the formation of the interventricular septum,[1] or to persistence of the intertrabecular spaces in the muscular part of the septum.[2] Functionally, they create pathways for blood to pass from the chamber with higher pressure to one with lower pressure with resultant hemodynamic and consequential anatomic alterations.

This report is based on a correlation of anatomic and hemodynamic data obtained during open heart surgery and systematic preoperative cardiac catheterization. The specific aims are to determine how the different anatomic facets of this disease find hemodynamic expression and how hemodynamic data may be used to gain insight into anatomic features.

MATERIAL AND METHODS

The data come from a review of twenty-six patients with isolated ventricular septal defect studied by cardiac catheterization and subsequently subjected to open-heart operations. Figure 1 shows the classification used in the localization of the defects. The maximum cardiac diameter (in cm.) in each case was measured from preoperative teleroentgenograms. The index or ratio of size of defect (S.D.) to cardiac diameter (C.D.) was calculated. Catheterization data included right ventricular and pulmonary artery systolic and diastolic pressures and shunt flow. Shunt flow was expressed as per cent of total pulmonary blood flow rather than actual measured shunt flow in liters/min. or cc./min., as this provided a basis for comparison of patients with widely different absolute cardiac outputs. Per cent shunt flow was calculated as follows:

$$\textit{per cent S.F.} = \frac{P.F. - Sys.\ F.}{P.F.} \times 100$$

where per cent S.F. = per cent shunt flow, P.F. = pulmonary flow and Sys. F. = systemic flow, or:

$$\textit{per cent S.F.} = 1 - \frac{BA - PA}{BA - RA} \times 100$$

where BA = oxygen content in brachial or femoral artery, PA = oxygen content in pulmonary artery and RA = oxygen content of mixed right auricular blood.

The patients were divided into two groups, one group comprising those with defects less than 2 cm. (Table I, Group A) and the other group comprising those whose defects were 2 cm. or more in diameter (Table I, Group B). In each group, the age, cardiac diameter, index of size of defect to cardiac diameter (S.D./C.D.), location of the defect and hemodynamic data were considered. Correlations were then established between the anatomic and hemodynamic data.

RESULTS

Right Ventricular Pressures and Shunt Flows: Average values of these measurements were considerably higher in patients with large defects, although means of ages and cardiac diameters were nearly equal (Table I).

Location of Defects: All twenty-six defects involved the membranous septum; in two patients an isolated defect was also present in the muscular septum. By the classification used (Fig. 1), no correlation could be established between location of the defect and the hemodynamic data.

Right Ventricular Pressure and Size of Defect:

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TABLE I
Data in Twenty-Six Patients with Ventricular Septal Defects

Case No.	Age (yr.)	Size of Defect (Diameter in cm.)	Cardiac Diameter (cm.)	Index (Size of Defect/Cardiac Diameter)	Location of Defect*	Pressures (mm. Hg) Right Ventricle	Pressures (mm. Hg) Pulmonary Artery	Shunt Flow (per cent)
Group A: Patients with Defect Less than 2 cm. in Diameter								
1	4	1.0	9.2	0.11	MSA	33/1	26/13	52
2	4	0.5	9.0	0.06	MSA	34/4	26/9	51
3	5	1.5	10.2	0.15	MSA	45/0	42/10	59
4	5	1.0	8.6	0.12	MSA	38/0	25/12	53
5	5	1.0	9.0	0.11	MSP	37/5	29/15	42
6	7	1.0	10.5	0.10	MSA	57/0	44/14	60
7	9	1.5	9.8	0.15	MSA	68/2	68/24	70
8	9	1.3	10.6	0.12	MSA (1 cm.) MUSC (0.3 cm.)	42/1	29/12	37
9	11	1.0	12.8	0.08	MSA	40/0	28/8	59
10	12	1.5	11.0	0.14	MSA	60/8	56/15	55
11	19	1.5	15.8	0.10	MSA	38/2	28/10	57
Averages	8.2	1.2	10.18	0.111	...	45/2	36.3/13	4.95
Group B: Patients with Defect 2 cm. or More in Diameter								
12	2	2.0	7.9	0.26	MSA (1 cm.) MSP (1 cm.) (fimbrinated)	80/12	88/48	48.1
13	2	2.0	10.0	0.20	MSM	54/-4	52/20	69
14	2	2.0	9.8	0.20	MSM	80/6	86/40	70
15	4	2.0	10.2	0.20	MSA	88/6	80/46	65
16	4	2.0	10.6	0.19	MSM	90/0	74/40	67
17	5	2.0	10.3	0.20	MSP	110/0	108/50	68
18	6	2.5	11.0	0.23	MSP	80/4	80/34	66
19	6	2.0	11.1	0.18	MSM	67/-7	65/42	70
20	6	2.0	13.0	0.15	MSP	98/2	92/52	66
21	7	2.0	10.8	0.19	MSA	105/2	110/45	48
22	7	2.0	8.7	0.22	MSA (1 cm.) MUSC (1 cm.)	36/-3	40/7	59
23	9	2.0	10.5	0.19	MSM	90/10	85/30	69
24	11	2.0	11.3	0.18	MSP	85/7	75/32	68
25	12	2.0	11.4	0.18	MSM	76/4	80/40	67
26	28	2.5	14.8	0.17	MSM	68/6	68/32	60
Averages	7.43	2.07	10.76	0.192	...	83.6/3.4	78.9/46.5	64.1

* MSA: defects involving anterior portion of the membranous septum.
MSM: defects involving mesial or entire membranous septum.
MSP: defects involving posterior portion of membranous septum.
MUSC: defects involving muscular septum.

A positive correlation between the size of the defect and right ventricular systolic pressure was noted but with a fairly wide scatter. However, inspection indicates that all patients but two with defects 2 cm. or more in diameter had right ventricular systolic pressures higher than 60 mm. Hg.

Right Ventricular Pressure and Index of Size of Defect: Correlations between the right ventricular systolic pressure and the index of size of

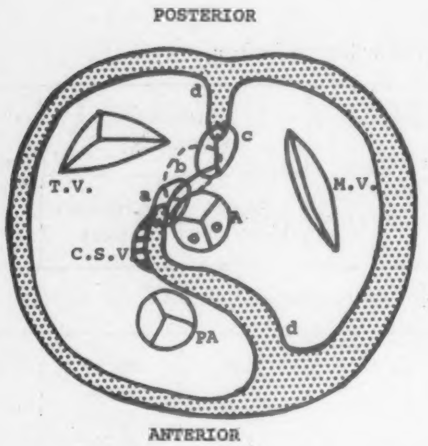

FIG. 1. Localization of ventricular septal defects. The heart is schematically represented in the transverse plane at the level of the membranous septum. a: defects involving the anterior portion of the membranous septum. b: defects involving the mesial or entire membranous septum. c: defects involving the posterior portion of the membranous septum. d: defects involving the muscular septum. PA = pulmonary artery; A = aorta; TV = tricuspid valve; MV = mitral valve.

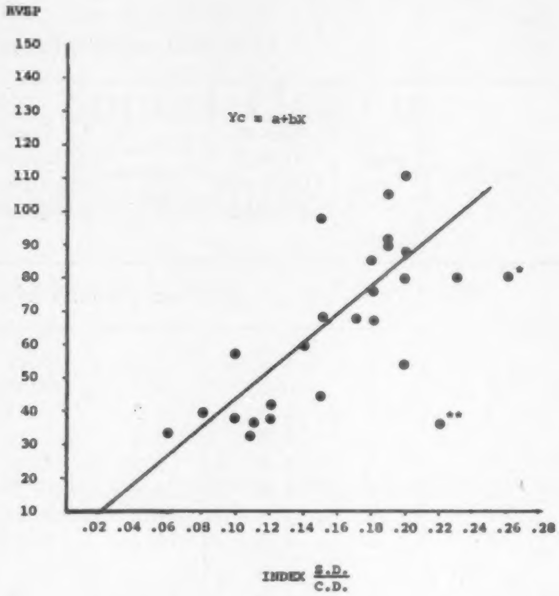

FIG. 2. Correlation between the right ventricular systolic pressure (RVSP) and the index size of defect (diameter of defect in cm.) over the cardiac diameter (maximum cardiac diameter in cm.). The coefficient of correlation (r) is 0.78. * = Case 12; ** = Case 22.

defect is shown in Figure 2. Correlation is apparent and scatter is less than in the association of right ventricular systolic pressure with absolute size of defect.

The coefficient of correlation (r) is 0.78 and the "p" value <0.001. The regression equation of these data indicates that index of size of 0.15 or over will usually be associated with a right ventricular systolic pressure of 60 mm. Hg or more.

These calculations did not include Cases 12 and 22 (Table I, Group B) as they were considered as not representative of the group. In one patient (Case 12), the defect was multiply fenestrated and in the other (Case 22), there were two defects of equal size, one situated in the anterior portion of the membranous septum, the other in the muscular septum. As identified in the scatter diagram (Fig. 2), both cases deviate widely from the regression line calculated for the remaining data.

Right Ventricular Pressure and Relative Shunt Flow: By plotting right ventricular systolic pressure against relative shunt flow the data distribute parabolically (Fig. 3). Dividing the parabola into five segments (criteria for segmentation indicated in each segment) demonstrates an association between anatomic and clinical states.

Segment 1 (shunt flow <50 per cent and right ventricular systolic pressure <60 mm. Hg) included two children five and nine years old. The defects were respectively 1.3 (0.3 cm. of which was in the muscular septum) and 1 cm. in diameter. Clinically, one patient had slight dyspnea on exertion and the other was asymptomatic. Their electrocardiograms were not remarkable except for slight axis shift to the left (SÂQRS in the frontal plane of +20 degrees) in one. X-ray films of the chest showed slight increases in lung vascularity in both.

Segment 2 (shunt flow >50 per cent and right ventricular systolic pressure <60 mm. Hg) included ten patients whose ages ranged from two to nineteen years (mean 7.6 years) and in whom mean size of defect was 1.3 cm. Symptomatology varied from slight dyspnea on exertion to none. SÂQRS in the frontal plane ranged from zero to +95 degrees and the electrocardiographic diagnoses included normal, combined ventricular overloading, left ventricular overloading (a majority) and right bundle branch block. X-ray films of the chest showed left ventricular hypertrophy in nine patients and combined ventricular hypertrophy in one patient. Lung vascularity was described as slightly to moderately increased in the majority of patients.

Segment 3 (shunt flow >50 per cent and right ventricular systolic pressure 60 to 90 mm. Hg) included nine patients whose ages ranged from

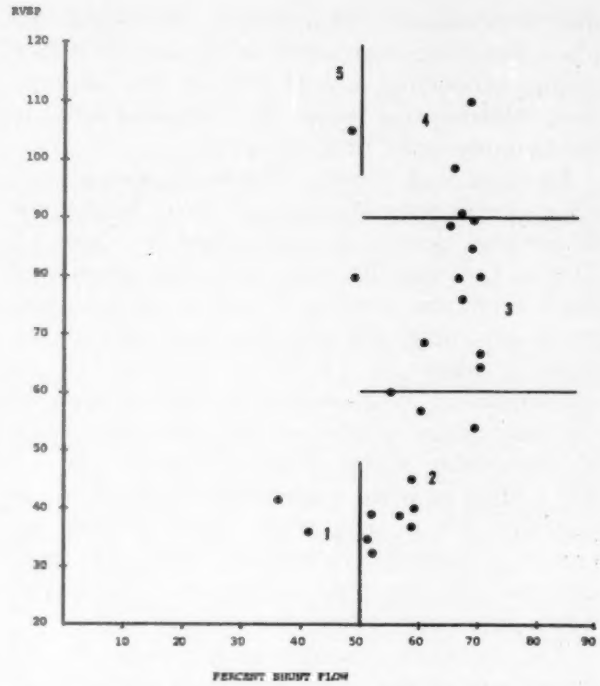

FIG. 3. Relationship between right ventricular systolic pressure (RVSP) and per cent shunt flow (shunt fraction of total pulmonary blood flow). A parabolic distribution is evident. See text for details of segments 1 to 5.

two to twenty-eight years (mean 8.9 years) and in whom mean size of defect was 2.05 cm. Seven were digitalized prior to admission to the hospital because of symptoms of congestive heart failure. Two patients were asymptomatic. SÂQRS in the frontal plane ranged from +90 to +150 degrees; the majority had an electrocardiographic diagnosis of combined ventricular overloading. X-ray films of the chest showed combined ventricular hypertrophy and increased pulmonary vascularity in all.

Segment 4 (shunt flow >50 per cent and right ventricular systolic pressure >90 mm. Hg) included four patients; their ages were from four to nine years (mean 6 years), and mean defect size 2 cm. Two patients were asymptomatic and of these one had been taking digitalis since infancy; one had slight exertional dyspnea and the other had cyanosis on exertion. SÂQRS in the frontal plane ranged from +120 to +150 degrees and electrocardiographic diagnoses of combined, predominantly right, ventricular overloading were made in all. X-ray films of the chest showed combined ventricular hypertrophy and increased lung vascularity in all.

Segment 5 (shunt flow <50 per cent and right ventricular systolic pressure >90 mm. Hg) consisted of one patient (Case 21) aged seven years, whose defect was 2 cm. This child was asymptomatic on admission but had been previously digitalized. SÂQRS was +120 degrees in the frontal plane and the electrocardiographic diagnosis was combined, predominantly right, ventricular overloading. X-ray films of the chest showed right ventricular hypertrophy. A biopsy of the lung (performed during the heart operation) showed medial hypertrophy, vascular dilatation and marked intimal fibrosis in the pulmonary arterioles (Fig. 4). Postoperatively, an infection developed at the operative site and later an aneurysm of the right ventricle appeared which was excised. She died two months after the first operation. Unfortunately no autopsy was performed.

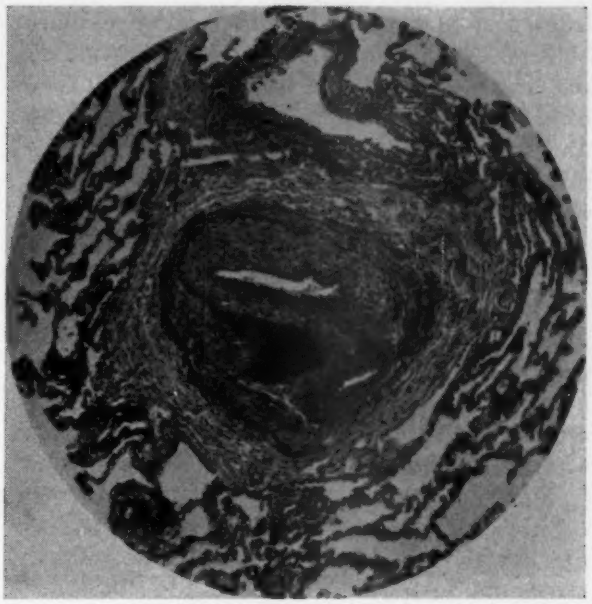

FIG. 4. A section of the biopsy of the lung in Case 21 (Table I, Group B), showing a medium sized pulmonary artery with medial hypertrophy, marked intimal fibrosis and elastosis of the internal elastic lamina (Van Gieson's stain × 400).

COMMENTS

ANALYSIS OF ANATOMIC FACTORS

Size of the Defect: In 1949, Selzer[3] reviewed the literature on ventricular septal defect, analyzed twelve patients who had come to autopsy and concluded that size of the defect is the major determinant of hemodynamic status. He later associated defects larger than 1.5 cm. in diameter with an elevated right ventricular systolic pressure.[4] Becu et al.,[7]

from a similar survey of fifty patients, shared Selzer's opinion on the relative importance of size of the defect. The present study, based on direct *in vivo* measurements, shows that size of the defect is indeed a major factor in determining the degree of hemodynamic alterations.

This relationship is determined by two main factors: (1) the resistance of a defect is inversely proportional to its size; thus, with a constant pressure gradient a larger defect will allow a greater shunt flow than a smaller one, and (2) larger defects are commonly associated with increased pulmonary resistance due to pulmonary arteriolar changes that may be congenital and acquired.[5]

However, absolute size of defect is less significant than its ratio to heart size as a determinant to cardiac dynamic alterations. A "small" defect in a heart of large volume will, with equal chamber pressures, allow as much absolute shunt flow as the same defect in a small heart, but with far less serious consequences. The validity of this assumption is indicated by the satisfactory correlation shown in Figure 2 between the right ventricular systolic pressure and the index of the size of the defect, using the diameter of the defect and the maximum cardiac diameter as an approximation of heart volume.

Location of the Defect: The relationship of the location of the defect to the hemodynamics and clinical findings has been controversial. Taussig,[6] in classifying ventricular septal defects as high and simple defects, claimed that the former had a more profound effect on pulmonary circulation than the latter. Selzer,[3] using his own classification, found no correlation of location to cardiac dynamic alterations. In agreement with this are Becu et al.[7] and Zacharioudakis et al.[8] Warden et al.,[9] however, from surgical observations of 120 cases of ventricular septal defects, considered that the anatomic relationship of the defect to the orifice of the pulmonary artery is just as important a factor as size.

In our series, defects of the membranous septum had equivalent effects, varying with size and independent of location. Isolated defects located in the muscular septum behaved differently. This is exemplified by Case 22 (Table I, Group B) where there were two defects of equal size, one of which was located in the muscular septum. Hemodynamic equivalents of these defects correspond only to those of the membranous septal defect. A logical explanation is the contraction of a muscular defect during ventricular systole and, on this assumption, effective size rather than location *per se* is the hemodynamic determinant.

Character of the Defect: This factor also primarily concerns resistance to shunt flow. A multiple fenestrated defect, as exemplified by Case 12 (Table I, Group B), will offer more resistance than a circular defect of equivalent cross-sectional area and will therefore have less hemodynamic effect.

Character of the Pulmonary Vessels: Lesions of the pulmonary vessels are anticipated in cases of ventricular septal defect whenever the defect is large or when a substantial shunt flow has persisted for a long time. Such lesions increase pulmonary arteriolar resistance and, consequently, the right ventricular systolic and mean pulmonary artery pressures.

The histologic changes which occur in the pulmonary arteries and arterioles are progressive in character. Heath and Edwards[10] described six grades of structural changes varying from medial hypertrophy in arteries and arterioles to intimal fibrosis, generalized vascular dilatation, appearance of plexiform and angiomatoid lesions and necrotizing arteritis.

ANALYSIS OF HEMODYNAMIC EQUIVALENTS

Right Ventricular Systolic Pressure: Elevations of right ventricular systolic pressure in the presence of a ventricular septal defect are directly related to the magnitude of the shunt flow and to the degree of pulmonary resistance. It can be used to estimate the relative size of the defect (by applying the regression equation, Fig. 2) and with the maximum cardiac diameter, a prediction of the absolute size may be ventured.

Pulmonary Artery Systolic Pressure: In uncomplicated ventricular septal defects, this value should approximate right ventricular systolic pressure. A gradient (right ventricular systolic pressure minus pulmonary artery systolic pressure) less than 20 mm. Hg is considered an expression of a functional pulmonic stenosis.[11]

Mean Pulmonary Artery Pressure: This value reflects the force that causes blood to flow across the pulmonary vascular bed; hence, it is a function of the amount of pulmonary flow and total pulmonary resistance.

Pulmonary Arteriolar Resistance: This value can

be calculated[12] as dynes second cm.$^{-5}$ by the formula:

$$PAR = \frac{(P.A.m - P.C.m) \times 1{,}332}{C.O./60}$$

where P.A.m = mean pulmonary artery pressure, P.C.m = mean pulmonary capillary pressure, C.O. = cardiac output in liters/min., and 1,332 = conversion factor of mm. Hg to dynes/cm.[2]

Normally, pulmonary arteriolar resistance is about one sixth or less of the peripheral resistance. With increased pulmonary flow, the pulmonary arterioles passively distend,[13] decreasing the proportion between resistance and flow. In large defects, lesions of the pulmonary arterioles obstruct the pulmonary blood flow and increase resistance which ultimately becomes fixed. Such a progressive increase in pulmonary arteriolar resistance may eventually bring it to levels of the order of peripheral resistance or greater.

Shunt Flow: This represents the amount of blood passing through the defect per unit time. It is dependent on the resistance of the defect and the pressure gradient between the left and right ventricles. Large shunt flows imply large defects or very high pressure gradients, and small shunt flows small defects or low pressure gradients. By correlating shunt flow with right ventricular systolic pressure a parabolic curve becomes evident which, when divided into five segments (Fig. 3), suggests the anatomic and clinical status of cases within each segment.

Segment 1 includes patients with small defects (1 cm. or less in diameter) whose clinical manifestations correspond to "maladie de Roger." Surgical repair of defects in patients who fall into this category is not mandatory, since these patients are most likely to do well throughout life. The only medical care indicated would be prophylaxis of bacterial endocarditis.

Segment 2 includes patients with moderately large defects (1 to 1.5 cm. in diameter) and normal or decreased pulmonary resistance. Clinically, they manifest signs and symptoms of increased pulmonary blood flow and often slight left ventricular preponderance. Surgical repair is definitely indicated since symptomatology is directly related to the shunt flow. These patients are usually good surgical risks.

Segment 3 includes patients with large defects (2 cm. or more in diameter) and normal or slightly elevated pulmonary resistance. Such patients show signs and symptoms of right and left ventricular overloading with definite pulmonary congestion. Surgical repair is indicated although they may be poor surgical risks because of cardiac failure.

Segment 4 includes patients with large defects (2 cm. or more in diameter), increased pulmonary resistance due to pulmonary arteriolar lesions and associated right ventricular hypertrophy. Such patients often appear to be well compensated. Surgery is indicated with the aim of correcting the shunt and remitting the lesions of pulmonary hypertension.

Segment 5, if extended, crosses the "Y" axis as would occur in Eisenmenger's complex. It includes patients with large defects (2 cm. or more in diameter) and large increases in pulmonary resistance. These manifest a state of borderline right cardiac failure and cyanosis, the latter a result of bidirectional or reversed shunt flow. Surgical repair is not feasible for the following reasons: (1) The pulmonary arteriolar changes at this phase are probably irreversible (grades 5 and 6),[10] (2) The magnitude of the shunt flow is less significant than the altered pulmonary circulation, and (3) In patients with bidirectional or reversed shunt flow, sudden closure of the defect may precipitate fatal right-sided failure.

PATHOLOGIC PHYSIOLOGY

Anatomic-hemodynamic correlation in congenital heart disease is usually fraught with the difficulty of analyzing interdependent factors in a continuously dynamic organ. In ventricular septal defects, cause and effect relationships are better comprehended if the heart is schematically represented as a twin-barrelled fluid pump (Fig. 5). In this figure are shown pressure-flow relationships *in a normal heart* (Fig. 5, I). Fluid is pumped from chamber A into vessel "a" by a piston Fa against a low resistance Ra and emptied into chamber B. Fluid in this chamber is pumped into "b" against a high resistance Rb and emptied into A. Both sides pump simultaneously, pressure in A is less than in B, but the amount of flow in "a" and "b" are equal. Peculiarities of the system are the distensibility (within certain limits) of the chambers, thus varying their capacities, the ability of the pistons to vary their driving force with limitations depending upon the load (mass of fluid to be ejected and resistance encountered) and the fluctuating resistance in Ra which be-

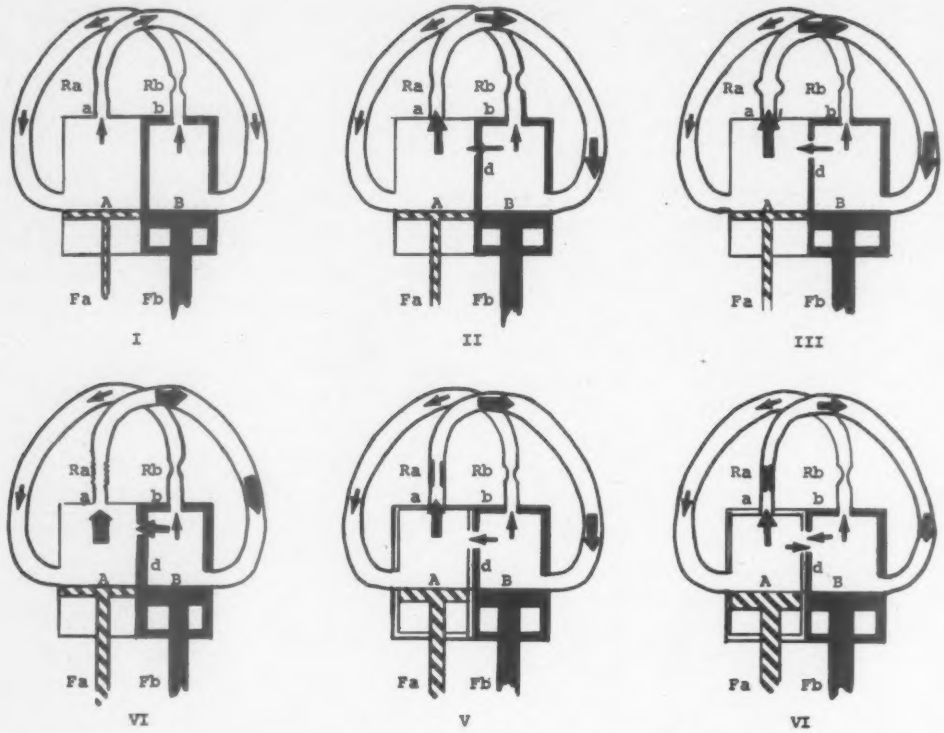

FIG. 5. The heart is schematically represented as a twin-barrelled fluid pump. A represents the right ventricle; B represents the left ventricle; Fa represents the force of right ventricular contraction; Fb represents the force of left ventricular contraction; a represents pulmonary circulation; b represents systemic circulation; Ra represents pulmonary resistance; Rb represents systemic or peripheral resistance; d represents the defect in interventricular septum. Arrows indicate direction and magnitude of flow. See text for details of pressure-flow relationship in I to VI.

comes lower with increased flow up to a certain limit beyond which resistance rises with further increments of flow.

Creation of a relatively small aperture or defect between A and B (Fig. 5, II), will allow fluid to flow from B to A. The amount of shunt will be delimited by the high resistance of the small defect despite the high pressure gradient. On ejection, flow through "a" will be slightly increased over "b" but resistance drops down in Ra, so the pressure is not increased in A. The amount of fluid reaching B will be slightly greater than in A just prior to ejection. This characterizes the anatomic-hemodynamic relationship of the patients in segment 1 of Figure 3.

If the defect is made a little larger (Fig. 5, III), its resistance to flow decreases and the amount of shunt through it will increase since there is little or no change in the pressure gradient. The amount of flow in "a" becomes greater, but resistance in Ra also decreases, so the pressure in A remains the same, or it may become slightly increased as a result of the increased volume of fluid being ejected. The amount of fluid reaching B is increased, overloading this chamber just before ejection ("diastolic overload"). This characterizes the anatomic-hemodynamic relationship of the patients in segment 2 of Figure 3.

If the defect is made still larger (Fig. 5, IV), the chain of events will simulate the preceding example except that the shunt flow through the defect is further increased. At this point, the distensibility of Ra may have reached its limit and further increments of flow will then increase the resistance. This, combined with the increased magnitude of shunt flow into A will raise the pressure in this chamber. There is also further increase in the volume of fluid reaching B and as a result, both chambers are being overloaded, B before ejection (diastolic) and A during ejection (systolic). This characterizes the anatomic-hemodynamic relationship of patients in segment 3 of Figure 3.

If the size of the defect remains the same as in the preceding example *but the resistance in Ra is increased* (Fig. 5, V), the pressure in A is further increased. The pressure gradient then de-

creases and therefore the shunt flow is also decreased. At any moment in time that the pressure in A equals B, the direction of the shunt flow will depend upon the resistance present in Ra and Rb. This characterizes the anatomic-hemodynamic relationship patients in segment 4 of Figure 3.

If the size of the defect remains the same but there is further increase in resistance at Ra (Fig. 5, VI), so that it equals Rb or even supercedes it, the pressure in A will equal B or may become higher, so that the shunt flow may be reversed in direction. In this instance, the defect itself may act as a safety valve to keep the pressure in A, originally designed to function as a low pressure chamber, from becoming excessively high. By closing the defect at this point, A as a pump may completely fail. This characterizes the anatomic-hemodynamic relationship of patients in segment 5 of Figure 3, and demonstrates why surgery is not indicated or is even contraindicated if there is a reversal of shunt flow.

There are probably *other physical factors* such as acceleration and velocity which have not been considered that may also affect anatomic-hemodynamic relationships, but considering these factors with lack of their quantitative values may lead only into flights of uninhibited speculations. In this presentation, discussion of the pathologic physiology of ventricular septal defects has been confined to correlation of salient factors.

Summary

Previous associations between size and location of ventricular septal defects and hemodynamics have been based on antemortem physiologic and postmortem anatomic observations. The present study is based on preoperative and operative observations *in vivo* in twenty-six patients.

Size of defect is shown to be the major determinant of hemodynamic abnormality. The index of relative size (measured diameter of defect/maximum cardiac diameter) shows a good correlation with right ventricular systolic pressure; the regression of this correlation enables approximate prediction of defect size.

Relative shunt flow (shunt fraction of pulmonary blood flow) distributes parabolically in relation to right ventricular systolic pressure. A plot of this distribution can be divided into five segments. These demonstrate correspondence of clinical and anatomic findings:

Segment 1 (shunt flow < 50 per cent; right ventricular systolic pressure < 60 mm. Hg): diameter of defect 1 cm. or less; corresponds to "maladie de Roger."

Segment 2 (shunt flow > 50 per cent; right ventricular systolic pressure < 60 mm. Hg): defects 1 to 1.5 cm. in diameter; increased pulmonary flow with left ventricular overload.

Segment 3 (shunt flow > 50 per cent; right ventricular systolic pressure 60 to 90 mm. Hg): defects 2 cm. or more in diameter; pulmonary congestion and combined ventricular overloading.

Segment 4 (shunt flow > 50 per cent; right ventricular systolic pressure > 90 mm. Hg): defects 2 cm. or more in diameter; clinically compensated but with right ventricular overloading.

Segment 5 (shunt flow < 50 per cent; right ventricular systolic pressure > 90 mm. Hg): defects 2 cm. or more in diameter; imminent cardiac failure with severe right ventricular hypertrophy. Surgical repair is indicated for patients in segments 2, 3 and 4.

The data clarify suggested mechanisms in ventricular septal defects and provide a basis for predictions of defect size and operability.

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References

1. De la Cruz, M. V., Christie, F. C., Olea, J. P., Anselmi, G. and Reinhold, M. Classification anatomo-embryologica de las comunicaciones interventricular aisladas. *Arch. Inst. cardiol. México*, 29: 195, 1959.
2. Gould, S. E. Pathology of the Heart. Springfield, Ill., 1953. Charles C Thomas.
3. Selzer, A. Defect of the ventricular septum. Summary of twelve cases and review of the literature. *Arch. Int. Med.*, 84: 798, 1949.
4. Selzer, A. Defects of the cardiac septum. *J. A. M. A.*, 154: 129, 1954.
5. Edwards, J. E. Functional pathology of the pulmonary vascular bed in congenital heart disease. *Circulation*, 15: 164, 1957.
6. Taussig, H. Congenital Malformations of the Heart. New York, 1947. Commonwealth Fund.
7. Becu, L. M., Fontano, R. S., DuShane, J. W., Kirklin, J. W., Burchell, H. B. and Edwards, J. E. Anatomic and pathologic studies in ventricular septal defects. *Circulation*, 14: 349, 1956.
8. Zacharioudakis, S. C., Terplan, K. and Lambert, E. C. Ventricular septal defects in the infant age group. *Circulation*, 16: 374, 1957.
9. Warden, H. E., DeWall, R., Cohen, M., Varco,

R. L. and Lillehei, C. W. A surgical-pathological classification for isolated ventricular septal defects and for those in Fallot's tetralogy based on observations made in 120 patients during repair under direct vision. *J. Thoracic Surg.*, 33: 21, 1957.

10. Heath, D. and Edwards, J. E. The pathology of hypertensive pulmonary vascular disease; a description of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects. *Circulation*, 18: 533, 1958.

11. Kjellberg, S. R., Mannheimer, E., Rudhe, M. and Jonsson, B. Diagnosis of Congenital Heart Disease. Chicago, 1955. Year Book Publishers, Inc.

12. Gorlin, R. and Gorlin, M. E. Hydraulic formula for calculation of the area of the stenotic mitral valve, other valves, and central circulatory shunts, *Am. Heart J.*, 41: 1, 1951.

13. Motley, H. L. The pulmonary circulation. In Intra Vascular Catheterization. Edited by Zimmerman, H. A. Springfield, Ill., 1959. Charles C Thomas.

Clinical Findings in Ventricular Septal Defects*

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To describe completely the clinical manifestations of ventricular septal defects, it would be necessary to encompass nearly all of the manifold findings in the field of congenital heart disease. In no single cardiac anomaly can the findings vary so widely from the extremely mild and insignificant to the most severe and malignant. The great variation in clinical findings is dependent primarily upon four factors: (1) the size of the defect; (2) the amount of pulmonary vascular resistance; (3) associated defects; and (4) the location of the defect in the septum.

Factors Controlling Clinical Findings

The first factor, *the size of the defect*, hardly merits comment since it is readily appreciated that through small defects only small shunts and slight pressure transmission can occur. Likewise, the converse is true for large defects. When the size of defects is described the size of the heart should also be kept in mind, since small openings in infants may result in the same findings as larger openings in adults. The defects vary from 1 to 15 mm. in diameter in infancy and in early childhood,[1] while in older children and adults they may vary from 0.5 to 3 cm. Accordingly, Selzer[2,3] has reasoned that the relative size of the defect to the size of the aortic orifice is the most important factor and that the pressure gradient between the two ventricles may disappear when the defect is larger than half the size of the aortic orifice.

When the defect is not small, the most important factor controlling pulmonary artery pressure and the amount of shunting is *pulmonary vascular resistance*. When this is low (e. g., 2 units) the amount of left-to-right shunting will be as much as the size of the defect will allow with a large pressure gradient. When pulmonary vascular resistance is increased, the pressure in the pulmonary artery will increase and the size of the shunt, therefore, will decrease. In situations where equal pulmonary and systemic pressures exist, large left-to-right shunts can still occur if pulmonary vascular resistance is still less than it is in the systemic circulation. If pulmonary resistance becomes marked (12 or more units) then the shunt may be from right to left and not from left to right.[4] In such a situation, right-to-left shunting can occur even through defects not considered to be "large."

The third factor, *associated defects*, can obviously alter the manifestations of this anomaly. This is particularly true when seen with pulmonary stenosis and when the defect is a so-called endocardial cushion defect associated with deformities of the mitral and tricuspid valves. This will be discussed briefly later.

The fourth factor, *the site of the defect*, is unquestionably the least important. It has not been established, but is certainly conceivable from previous work on ventricular contraction,[5] that should the defect lie in the muscular portion of the septum, ventricular contraction could cause a decrease in the size of the defect and therefore less shunting would occur than if the same sized defect were in the membranous portion. Other factors being equal, the site of the defect does not control the amount of shunting. This is true specifically in its relationship to an "overriding" aorta since the direction of the shunting is controlled primarily by the second factor mentioned, pulmonary vascular resistance. In addition, endocardial cushion defects can be associated with deformities of the atrioventricular valves and accordingly can alter the clinical picture presented by a ventricular septal defect, as previously mentioned. The site of the defect can be additionally significant, in that it may control the site of a bacterial endocarditis, since bacterial endocarditis is most frequently seen with defects in the membranous portion.

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Clinical Groups

The situation in small infants is unique in that during the first year of life and particularly under the age of six months, infants may die from what would appear to be insignificant defects.[7] Beyond the period of infancy, however, ventricular septal defects tend to "stabilize" and, as suggested by Keith et al.,[1] fall into four rather distinct clinical groups dependent upon the controlling hemodynamic factors listed above. These four divisions, modified slightly, are as follows:

Group I: Small defects, a small left-to-right shunt and normal or near normal pulmonary artery pressure.

Group II: Considerably increased blood flow through the defect but with only slight pulmonary vascular resistance and therefore only a moderate increase in pulmonary artery pressure.

Group III: Increased pulmonary vascular resistance and marked increase in pulmonary vascular pressure to systemic or near systemic levels, but a predominantly left-to-right shunt.

Group IV: Pulmonary hypertension equal to systemic pressures and a predominant right-to-left shunt which may be sufficient to produce cyanosis.

It should be appreciated that it is frequently impossible to "categorize" a given patient into such a classification and that any patient may "progress" into the next group, dependent on the reaction of the muscular arteries in the lung. At this time there is no way of predicting which patients will show progressive changes.

GROUP I

Those patients with small defects are, fortunately, the largest group and comprise from 25[8,9] to 60 per cent of cases.[1] It is to this group that the term "Roger's disease" is classically applied to comply with the original description by Roger,[10] in 1879, of two asymptomatic patients with ventricular septal defects.

The defect is most usually recognized by the examining physician who discovers a murmur during a routine well-baby examination. The murmur is not so frequently detected in the immediate neonatal period as is the murmur of semilunar valve stenosis. When routine well-baby care has not been given, it is not unusual for a parent to detect a precordial thrill or actually hear the murmur and bring the infant to the doctor for this reason. They have either normal tolerance to exercise or a slight loss of tolerance with vigorous effort, at which time undue dyspnea may appear.

On physical examination these patients are of average size. During infancy and childhood, they exhibit a normal growth pattern. They are never cyanotic, even with exertion, and do not show clubbing or hyperemia of the digits. Since the shunt is small, cardiac hyperactivity is either slight or not readily detected and consequently little or no prominence of the left precordium is present. A mildly forceful apical thrust may be detected. The most striking finding on palpation, however, is a systolic thrill which is practically universally present. It is felt best along the lower left sternal border in the third to fifth intercostal space. If a thrill is felt higher along the left sternal border, it is more likely due to pulmonary stenosis. The thrill of ventricular septal defect is never felt in the suprasternal notch.

On auscultation a grade 4/6 to 6/6 harsh, systolic "regurgitant" murmur[11] is heard in every patient. It is best heard along the lower left sternal border at the site of the thrill and is widely transmitted over the chest. The transmission is often very good along both costal margins. The murmur is also heard well posteriorly in the lower half of the chest, but is not heard well high in the back or in the neck, as is the murmur of semilunar valve stenosis. An early diastolic murmur in the apical area due to rapid and large volume inflow across the mitral valve is infrequently heard (10 per cent)[7] because there is only a slight increase in pulmonary flow due to the left-to-right shunt. The second sound in the pulmonary area is normally split and is not remarkable except that it may be difficult to detect because of the holosystolic nature of the loud regurgitant murmur.

Prognosis: It is generally conceded that patients fulfilling the criteria for group I are capable of active lives without compromise of longevity.[12] Whether or not this lesion is actually as benign as suspected, however, will probably take another generation to answer, for we have not yet had the opportunity of following up such patients through a life span after the diagnosis is established by catheterization early in childhood. The principal challenge to life in these patients does not appear to be cardiac failure but rather bacterial endocarditis.

There is a genuine threat to the general well-

being of these patients which unfortunately is chiefly iatrogenic, but also propagated by well meaning family and friends. This is the unjustified prohibition from physical activity and the constant reminder that heart disease is present which ultimately results in psychologic crippling. It is my impression that this is less of a problem today than it has been in the past when such striking physical findings were more frequently interpreted as indicating serious cardiac disease.

GROUP II

In patients of this second group there is a large left-to-right shunt, slight pulmonary vascular resistance and moderate pulmonary hypertension primarily due to the large pulmonary flow. Because of the large left-to-right shunt, systemic flow may be compromised. As in group I, the presence of heart disease is discovered frequently at the time of a routine well-baby check by the detection of a murmur. Because infants in this group do not fare well, are frequently "feeding" problems, are often dyspneic at rest and readily acquire serious respiratory infections, medical attention is sought by the parents and the defect is discovered in this way.

As infants, they may show dyspnea at rest and exhibit fatigue with feedings and mild exertion. In some of these infants with large shunts left heart failure will develop and cause death. The heart failure may be masked by or complicated by a superimposed respiratory infection and thus be difficult to recognize. This possibility should always be strongly considered whenever one of these patients fails to respond promptly to treatment for pneumonia. If these infants survive beyond the first year of life, they characteristically improve, showing an increased tolerance to exercise, better growth and less susceptibility to respiratory infections. This is often quite dramatic. These children continue to have cardiac enlargement, but always amazing is the slight loss of tolerance to exercise they show.

It has been assumed that this improvement is due to an increase in pulmonary vascular resistance so that pulmonary flow is decreased. If this increase in pulmonary vascular resistance becomes sufficiently marked these patients then fall into group III.

On physical examination these patients almost universally show some retardation of growth. They are never cyanotic, even with exercise. Because of the marked cardiac hyperactivity a prominent precordium is always present. Since left ventricular output is increased, the left ventricle is large and hyperactive, so that a forceful apical thrust is readily seen and felt. A systolic thrill is practically always present, having the same characteristics as that described in group I.

On auscultation a grade 3/6 to 6/6 systolic regurgitant murmur is detected, as described under group II. With the large pulmonary flow that is common to these defects, the systolic murmur high along the left sternal border may assume a lower pitch and be more characteristic of an ejection murmur. There is an early low pitched diastolic murmur in the apical area in practically all these patients. This was found in 90 per cent of Wood's patients with a large pulmonary flow.[8] This murmur is due to a rapid flow of a large volume across the mitral ring in early diastole. This murmur should not be confused with the typical murmur of mitral stenosis, since it occurs early in diastole and is not accompanied by an opening snap or an accentuated first heart sound. A third heart sound is frequently heard in the apical area and is attributed to the rapid inflow of blood into the left ventricle in early diastole. The second sound in the pulmonary area is distinctly split and the pulmonic component may be moderately accentuated. A diastolic murmur of pulmonary incompetence is rarely heard in patients of this group.

Prognosis: As mentioned, the most difficult period for these patients is during infancy. A few die in cardiac failure, but most survive. Their survival is apparently aided by a compensating increase in pulmonary vascular resistance. A few of these patients may, in turn, have progressive changes in their small pulmonary arteries resulting in severe pulmonary hypertension. Just which patients will exhibit this change is something we are unable to identify at this time.

GROUP III

The third group comprises those patients who have marked pulmonary hypertension due to changes in the small pulmonary arteries, but who still have a predominant left-to-right shunt. These patients are usually severely ill and death from cardiac failure under one year of age may occur. They present the characteristic picture of the underdeveloped, asthenic, chronically ill patient commonly associated with

severe congenital heart disease. They are not cyanotic except with severe exertion or with pneumonia to which they are unduly susceptible. Hyperemia of the terminal portions of the digits, however, is common and typical for these patients with only mild peripheral desaturation.

On examination, there is always some left-sided precordial prominence. This is made more apparent by the characteristically thin habitus of these patients. There is a heaving action to the precordium due to hypertrophy of the right ventricle in addition to a mildly forceful apical thrust. Cardiac activity, thus, is different than in patients of group II in whom the left ventricle is the more hyperactive chamber. The precordial heave is often accompanied by a visible xiphoid impulse. A systolic thrill may be encountered, but is not characteristic for this group as it was for the preceding two groups. Next to the precordial heave the most striking finding is a diastolic tap felt along the upper left sternal border, due to the forceful closing of the pulmonary valve from marked pulmonary hypertension.

The most characteristic *auscultatory finding* is not a murmur in these individuals, but a loud, booming second sound in the pulmonary area. This is frequently so marked that the aortic component is overshadowed, making it difficult to detect the split in the second sound. Systolic murmurs, while still present at the same site, are usually not as intense and are of only grade 1/6 to 4/6 in intensity. They continue to be regurgitant in character, however. If pulmonary flow is sufficiently large, a diastolic murmur and a third heart sound may be detected in the apical area. A high pitched and usually faint (grade 1/6 to 2/6) diastolic murmur of pulmonary incompetence is frequently heard along the upper left sternal border (never along the right).

The pulse and systemic blood pressures are normal. When congestive failure is present it is predominantly right-sided and hepatic enlargement and venous distention can then be encountered along with peripheral edema.

Prognosis: Many of these patients die in infancy from congestive failure and pneumonia. They are nearly always markedly handicapped and it is unusual for them to survive beyond thirty years of age.

GROUP IV

In patients of the fourth group, the pulmonary vascular resistance is greater than systemic resistance and a right-to-left shunt occurs with a reduction in pulmonary flow. When the shunt is sufficient to produce cyanosis, the criteria for Eisenmenger's syndrome are fulfilled. The response of the pulmonary arteries to produce the necessary resistance for the marked pulmonary hypertension is characteristically present at birth or shortly thereafter. Consequently, patients in this group are cyanotic from birth or early infancy. Cyanosis is generally more common and also more pronounced in these patients than in those who acquire the Eisenmenger reaction after childhood. They are subject to the same complications as any patient with cyanotic congenital heart disease, namely, clubbing of the digits, polycythemia and cerebral thrombosis and abscess. It is also difficult to distinguish these patients from other cases of Eisenmenger's reaction in which there is severe pulmonary hypertension and a right-to-left shunt, either at the level of the atrium or ductus. They are markedly limited in tolerance to exercise. Cyanosis characteristically is increased with exercise since the pulmonary resistance prohibits an increased pulmonary flow with exercise and thereby the right-to-left shunt is increased.

On physical examination these patients present varying degrees of cyanosis, clubbing and facial suffusion. Retardation of growth is not so marked in these patients as in those of groups II and III. There is usually some precordial prominence, due to right ventricular enlargement, but this is likewise not so marked as in the preceding two groups, since these patients do not exhibit as much cardiac hyperactivity. Likewise, they do not present cardiomegaly to such a marked degree as those in groups II and III. A precordial lift, due to right ventricular hypertrophy, is readily detected on palpation. A thrill is practically never encountered. Pulmonary valve closure is readily felt along the upper left sternal border.

On auscultation the most striking finding is the markedly accentuated pulmonary component of the second sound which commonly is followed by a high pitched diastolic murmur of pulmonary incompetence. Rarely does this exceed grade 3/6 in intensity. A loud systolic ejection click usually is heard along the upper left sternal border and is followed by a grade 1/6 to 2/6 ejection murmur. A systolic murmur along the lower left sternal border is rarely encountered, since the right-to-left shunt never seems to effect enough turbulence to

become audible. Peripheral pulse and systemic blood pressures are normal.

Prognosis: When heart failure occurs it is classically "right heart" failure with typical findings. This is the usual mode of death in these patients.

Those who have a typical Eisenmenger syndrome at birth usually die by puberty, although patients have been known to survive beyond fifty years of age. Those who progress from group III to group IV usually die within a few years after the appearance of cyanosis.

Associated Congenital Lesions

It is my prime purpose to discuss ventricular septal defects without associated anomalies. However, it seems worthwhile to mention two frequently encountered clinical entities in which the ventricular septal defect is the predominant lesion. The first is the *endocardial cushion defect* which is a low atrial septal defect frequently combined with deformities of the atrioventricular valves, principally the mitral. The electrocardiogram gives a rather typical pattern for this type of defect and when seen with suggestive findings of mitral insufficiency in association with a ventricular septal defect, should alert attention to this possibility. This is of great importance now, when surgical repair of ventricular septal defects is becoming so common. Repair of such a defect entails a greater hazard than an uncomplicated septal defect.

The second combined lesion is that of the so-called *balanced, pink or acyanotic tetralogy of Fallot* in which the shunt is still predominantly left-to-right in spite of the pulmonary stenosis. The septal defect found in these patients is usually rather large and the pulmonary stenosis becomes a compensating feature of this entity. It should be strongly suspected if a loud systolic murmur is heard high along the left sternal border with good transmission high into the back and into the left infraclavicular area. Roentgenographic findings and an electrocardiogram will offer strong clues for the diagnosis.

Endocarditis

Bacterial endocarditis complicates the clinical picture in sufficient frequency so that a brief comment seems indicated. This complication is seen much more frequently with this defect than with other congenital anomalies according to Gelfman and Levine[6] (10.4 per cent as compared with 6.2 per cent for other congenital anomalies). It is seen characteristically in young adults and is unusually rare in early childhood and infancy. The reported incidence of as high as 40 per cent in patients coming to autopsy and an average of approximately 10 per cent in clinical patients is probably considerably higher than the actual incidence at this time. The use of antibiotics, particularly at times of dental extractions or other manipulative procedures or operations when a bacteremia is likely to occur, has unquestionably decreased the incidence.

Since the site of the endocarditis is most seen at points of trauma, it usually occurs on the margins of the septal defect, the septal leaflet of the tricuspid valve or on the ventral wall of the right ventricle where the "jet" through the defect would cause endocardial thickening and injury. Since the site of infection is in the right side of the heart, the embolic manifestations of petechiae and splenomegaly will not be seen with the same frequency as a "left-sided" lesion, such as endocarditis of the mitral or aortic valve.

Summary

The clinical findings in ventricular septal defects may vary from insignificant to severe. These findings are predominantly dependent on factors that control the hemodynamics through these defects. The two most important factors are (1) the size of the defect and (2) the degree of pulmonary vascular resistance. These factors vary in importance in different patients but generally combine to allow this anomaly to present four distinct clinical pictures with distinctive findings in each.

References

1. Keith, J. D., Rowe, R. D. and Vlad, P. Heart Disease in Infancy and Childhood. New York, 1958. The Macmillan Co.
2. Selzer, A. and Laquer, G. L. The Eisenmenger complex and its relation to the uncomplicated defect of the ventricular septum. Review of thirty-five autopsied cases of Eisenmenger's complex, including two new cases. *Arch. Int. Med.*, 87: 218, 1951.
3. Selzer, A. Defects of the cardiac septums. *J. A. M. A.*, 154: 129, 1954.
4. Wood, P. Pulmonary hypertension. *Mod. Concepts Cardiovas. Dis.*, 28: 513, 1959.
5. Rushmer, R. F. Cardiac Diagnosis, A Physiologic Approach. Philadelphia, 1955. W. B. Saunders Co.
6. Gelfman, R. and Levine, S. The incidence of acute and subacute bacterial endocarditis in

congenital heart disease. *Am. J. M. Sc.*, 204: 324, 1942.
7. Zacharioudakis, S. C., Terplan, K. and Lambert, E. C. Ventricular septal defects in the infant age group. *Circulation*, 16: 374, 1957.
8. Wood, P., Magidson, O. and Wilson, P. A. O. Ventricular septal defects with a note on acyanotic Fallot's tetralogy. *Brit. Heart J.*, 16: 387, 1954.
9. Nadas, A. Pediatric Cardiology. Philadelphia, 1957. W. B. Saunders Co.
10. Roger, H. Recherches cliniques sur la communication congenitale des deux coeurs, par inocclusion du septum interventriculaire. *Bull. Acad. Med. Paris*, 8: 1074, 1879.
11. Leatham, A. Splitting of heart sounds and a classification of systolic murmurs. In: Symposium on Cardiovascular Sound. II. Clinical Aspects. *Circulation*, 16: 417, 1957.
12. Taussig, H. Congenital Malformations of the Heart. New York, 1947. Commonwealth Fund.

The Auscultatory and Phonocardiographic Signs of Ventricular Septal Defects*

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AUSCULTATION and phonocardiography have been neglected too frequently in the evaluation of patients with congenital heart disease. The original report of Roger[1] clearly described the auscultatory findings in ventricular septal defect. The present report will attempt to show the usefulness of auscultation and phonocardiography in the diagnosis and differential diagnosis of the various forms of ventricular septal defect.

MATERIAL AND METHOD

Forty-four patients with ventricular septal defect were studied. The clinical diagnosis was confirmed by cardiac catheterization, operation, angiocardiography or necropsy. The physical findings were recorded in detail by an experienced physician, usually one of us. Phonocardiographic confirmation was obtained in every case. Particular attention was paid to the quality, intensity and duration of murmurs and the degree of splitting of the second heart sound.

Phonocardiograms were obtained with the Sanborn Twin-Beam or Tri-Beam phonocardiograph. A paper speed of 75 mm./sec. was used. A simultaneous carotid artery and/or jugular venous pulse was obtained in most instances. Lead II of the electrocardiogram was used as a reference tracing. Analysis of the second sound was made with the patient in full expiration. The aortic component of the second heart sound could be identified by its relation to the dicrotic notch of the simultaneous indirect carotid artery tracing allowing a delay of from 0.01 to 0.04 second. Both low and high frequency recording characteristics were utilized. Usually the high frequency recording proved to be the most satisfactory for analysis.

Cases of ventricular septal defects associated with dextroposition of the aorta and patent ductus arteriosus were not included among the forty-four patients studied but will be discussed later. A subdivision of the anatomic diagnosis in the forty-four patients studied is shown in Table I.

RESULTS

First Heart Sound: The first sound was usually of normal intensity and not conspicuously split (Fig. 1). It was of decreased intensity in only two of the forty-four patients. Its analysis was frequently made difficult by the close association of the systolic murmur to the first sound, but the phonocardiogram invariably demonstrated a normal first sound. Occasionally the first sound was exceptionally loud or soft at the apex. When the tricuspid and mitral components could be identified splitting was usually normal (up to 0.03 second). This could not be ascertained by the phonocardiogram in all instances because the murmur obscured the tricuspid component.

Second Heart Sound: There was marked variation in the intensity and degree of splitting of the second heart sound. In the patients with isolated ventricular septal defect and normal right-sided pressures, the pulmonary second sound could always be identified and was either of normal intensity or accentuated (Figs. 2 and 3). The aortic component was frequently buried in the pansystolic murmur so that clinical analysis of the degree of splitting was often difficult. However, in many patients both components could be heard over the aortic or pulmonary area. The phonocardiograms with carotid pulse tracings always allowed analysis of the degree of splitting, as even when the aortic component was buried in the murmur it could be estimated fairly accurately because of its relationship to the dicrotic notch. Slight to moderate splitting was the rule, but occasionally the split became single on deep expiration (Fig. 4).

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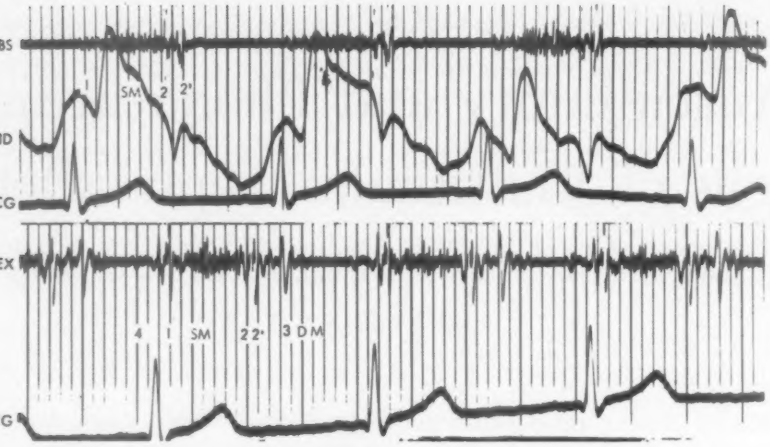

FIG. 1. Phonocardiogram in Case 8. At the apex (below) the first heart sound is of normal intensity and normally split. It is followed by a holosystolic murmur, a split second sound and a loud third heart sound. A short-mid-diastolic low frequency murmur follows the third heart sound. An atrial sound was recorded on the phonocardiogram but was not audible. At Erb's area the split second sound can best be appreciated. It varied from between 0.06 to 0.04 second but never became single as in the normal. In all illustrations the following symbols are used: 1 = first heart sound. 2 = second heart sound. When split, 2 = aortic component; 2′ = pulmonic component. 3 = third heart sound. 4 = fourth or atrial sound. Cl = systolic ejection click. SM = systolic murmur. DM = diastolic murmur. MA = mitral area. PA = pulmonary area. Jug = jugular venous pulse. Carotid = carotid artery pulse. TA = tricuspid area. HF = high frequency recording.

Of seven patients with pulmonary hypertension the pulmonary component was accentuated in all. In four of the seven, the second sound was more narrowly split than in the patients with normal pressures (Fig. 5). When the defect was associated with pulmonary stenosis, behavior was more like pure pulmonary stenosis in that there was wide and fairly fixed splitting with a diminished intensity of pulmonary closure observed in all four patients (Fig. 6).

The three patients with aortic regurgitation (Table I) had normal right-sided pressures and behavior was more like ventricular septal defect with normal pressures in regard to the degree of splitting and intensity of the second pulmonary sound.

Third Sound: An apical third or ventricular filling sound was heard and recorded in twenty-nine of the forty-four patients (Figs. 1 and 3). It was usually fairly well localized to the apical area and occurred on the phonocardiogram approximately 0.14 second after closure of the

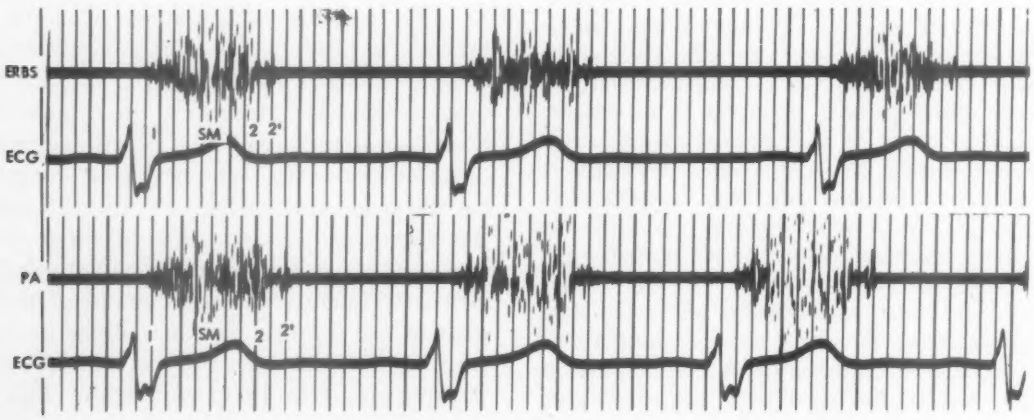

FIG. 2. Phonocardiogram in another patient (Case 14) with normal pressures. The second sound is of normal intensity and moderately split. The murmur is equally loud in the pulmonary area and Erb's area. It is diamond-shaped but of far greater importance is its pansystolic character.

TABLE I

Auscultatory and Phonocardiographic Findings in Forty-Four Cases of Ventricular Septal Defect

Case No.	Intensity of First Sound	Splitting of Second Sound (sec.)	Intensity of Second Sound	Third Sound	Ejection Sound	Fourth or Atrial Sound	Systolic Murmur	Diastolic Murmur
Ventricular Septal Defect with Pulmonary Stenosis								
1	N	0.04	D	0	+	0	Pan	0
2	N	0.06	D	+	0	0	Pan	0
3	N	0.05	D	+	0	0	Ejection	0
4	N	0.06	D	0	0	0	Pan	0
Ventricular Septal Defect with Aortic Insufficiency								
5	N	0.03	N	0	+	0	Pan	Aortic
6	N	0.02	N	0	+	0	Pan	Aortic
7	N	0.03	N	0	0	0	Pan	Aortic
Ventricular Septal Defect with Normal or Slightly Elevated Right Ventricular and Pulmonary Artery Pressures								
8	N	0.05	N	+	0	+	Pan	Apical
9	N	0.06	N	+	0	0	Pan	0
10	N	0.02	I	0	+	+	Pan	0
11	N	0.06	N	+	0	+	Pan	0
12	N	S	N	0	0	0	Pan	0
13	N	0.04	I	+	0	0	Pan	Pulmonary
14	N	0.05	I	0	+	0	Pan	0
15	N	0.06	I	+	0	0	Pan	Apical
16	N	0.03	I	+	0	0	Pan	0
17	N	0.05	I	+	0	0	Pan	Pulmonary
18	N	0.04	I	0	0	+	Pan	Apical
19	N	0.04	N	0	+	+	Pan	Apical
20	N	0.02	I	+	+	0	Pan	Pulmonary
21	N	S	N	+	0	0	Pan	0
22	N	S	I	+	0	0	Early	0
23	D	0.04	N	+	0	0	Pan	0
24	N	0.04	N	+	+	0	Pan	Apical
25	N	0.03	I	+	+	+	Pan	Apical
26	N	0.04	I	+	0	0	Pan	Apical
27	N	0.05	I	+	0	0	Pan	Apical
28	N	0.03	N	0	0	+	Pan	0
29	N	0.04	N	+	0	0	Pan	0
30	N	0.04	I	+	0	0	Pan	0
31	N	S	I	+	0	0	Pan	Apical
32	N	0.02	N	+	0	0	Pan	0
33	N	0.01	I	0	0	0	Pan	Pulmonary
34	N	0.03	N	+	0	0	Pan	Apical
35	N	0.04	I	+	+	0	Pan	Apical
36	N	0.04	I	+	0	0	Pan	Apical
37	D	0.04	N	0	0	0	Pan	0
Ventricular Septal Defect with Pulmonary Hypertension								
38	N	0.04	I	+	+	0	Pan	Pulmonary
39	N	0.03	I	+	+	0	Pan	0
40	N	0.01	I	+	+	0	Short, soft	Pulmonary
41	N	0.01	I	0	+	+	Short, soft	0*
42	N	0.01	I	+	0	0	Pan	0*
43	N	0.02	I	+	+	0	Pan	0
44	N	0.01	I	0	0	0	Short, soft	0

NOTE: N = normal. I = increased. D = decreased. + = present. 0 = absent. Pan = pansystolic. * = audible, not recorded. S = single second sound.

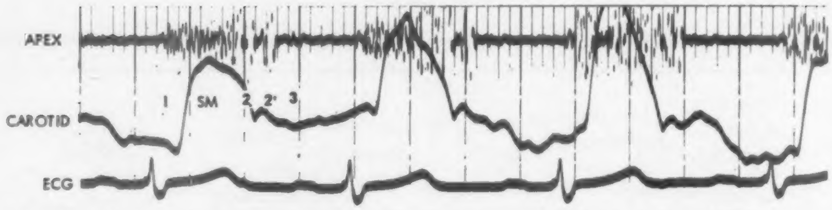

FIG. 3. Case 17. The systolic murmur is loud at the apex. The second sound is clearly split at the apex, indicating an increased intensity of the pulmonary closure. A third sound is present. In this case the carotid artery tracing is helpful in identifying the aortic second sound which is buried in the end of the systolic murmur and not audible.

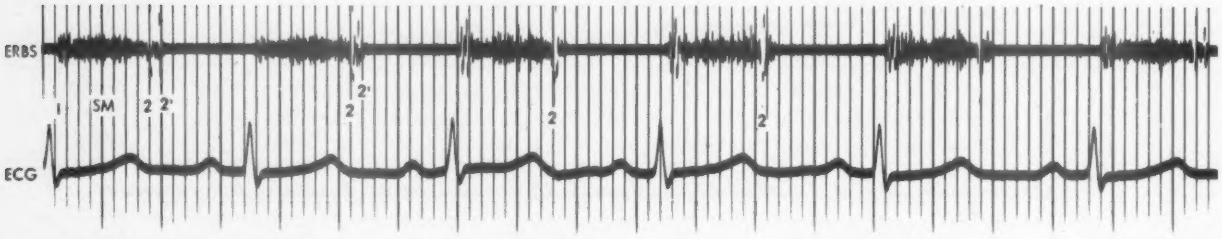

FIG. 4. Case 12. Phonocardiogram taken during quiet respiration demonstrating normal splitting of the second sound. The second sound, split on inspiration, gradually becomes single on expiration.

aortic valve. Of the seven patients with the highest pulmonary artery and right ventricular pressures, a third heart sound was present in only one despite the fact that there was a large left-to-right shunt in all.

Atrial or Fourth Sound: An atrial sound was recorded in the phonocardiogram in only seven

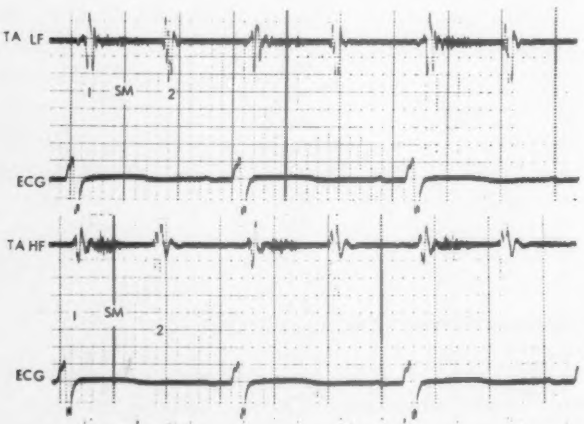

FIG. 5. Case 41. The effect of pulmonary hypertension on the auscultatory findings is clearly demonstrated in this phonocardiogram. The second sound is narrowly split and accentuated. The systolic murmur which was only of grade II intensity is short.

instances (Fig. 1). It was always of very low intensity and never audible.

Pulmonary Ejection Sound: An early systolic ejection sound caused by sudden distension of the pulmonary artery was observed in thirteen phonocardiograms (Fig. 7). It is distinctly less common in ventricular septal defect than in pulmonary stenosis or atrial septal defect, but its mechanism of production is similar. Five of the seven patients with pulmonary hypertension had ejection sounds demonstrated in the phonocardiogram. An aortic ejection sound was present in two of the three patients whose defect was associated with aortic insufficiency. Because the murmur commences with the first sound and may be of great intensity over the pulmonary area a click may not be appreciated by auscultation. Even in the phonocardiogram it is frequently difficult to be certain that there is an ejection sound or merely a high amplitude component of the murmur.

Systolic Murmur: The typical murmur is a harsh, high pitched, pansystolic murmur accompanied by a thrill. Such a murmur was present in forty patients (Figs. 1 to 4). It is maximal in the third to fourth intercostal space to the left of the sternum but occasionally is equally loud over the pulmonary area despite the absence of pulmonary stenosis. The murmur varied from being of equal intensity and pitch throughout systole (Fig. 3), to crescendo-decrescendo (and hence diamond-shaped

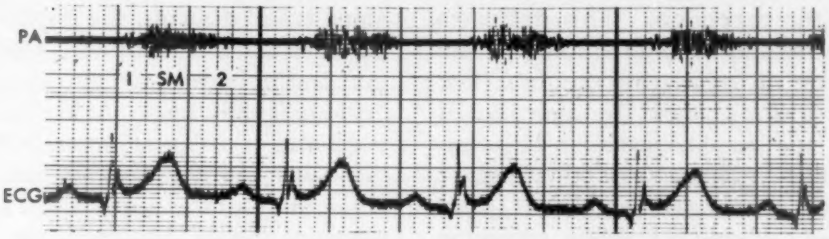

FIG. 6. Case 3. Ventricular septal defect with pulmonary infundibular stenosis. The second sound is diminished in the pulmonary area. The murmur commences after the first sound and ends before the pulmonary component of the second sound, suggesting that it is caused by the pulmonary stenosis.

(Figs. 2 and 7). So intense was the murmur that it obscured the heart sounds in many cases. Grading was of little value because the murmurs varied from grades II to V (on a scale of VI), but it was generally of grade III or louder. Although well heard at the apex it faded toward the axilla and back.

Patients with associated pulmonary stenosis could not be differentiated from those with isolated ventricular septal defect with certainty on the basis of the murmur alone even though a loud murmur and thrill over the pulmonary area was more likely. Usually the delayed diminished pulmonary closure was the most reliable sign of coexisting pulmonary stenosis (Fig. 6). Patients with marked pulmonary hypertension had less intense, shorter systolic murmurs (Fig. 5). In the three patients with the highest pulmonary artery pressures the murmur was the softest and was not holosystolic. In one patient with a small ventricular septal defect there was a short decrescendo systolic murmur over the tricuspid area.

Diastolic Murmurs: Three types of diastolic murmurs were observed. *The first type* (three cases) was a typical aortic diastolic murmur associated with aortic regurgitation. It was usually loud, blowing in character and maximal either at the aortic area, Erb's point or at the apex and was present in the three patients with aortic insufficiency. Occasionally a continuous murmur is produced which may simulate a patent ductus arteriosus or aortopulmonary septal defect, but its quality and timing are somewhat different. *The second type* (eight cases) was a pulmonary diastolic murmur similar to the Graham Steell murmur in quality, location and timing (Fig. 8). It was high pitched and blowing and often restricted to the pulmonary or Erb's area. It was observed on the phonocardiogram in two patients with pulmonary hypertension and heard in two cases in which the phonocardiogram failed to register

FIG. 7. Case 43. Ventricular septal defect with pulmonary hypertension. An ejection sound precedes the maximum intensity of the systolic murmur. The murmur is loud and diamond-shaped. There was no pulmonary stenosis.

the murmur. *The third type* of diastolic murmur (eleven cases) was a mid-diastolic, low pitched rumble at the apex (Fig. 1). It was invariably preceded by a third heart sound. This murmur is caused by torrential flow of blood across a normal mitral valve orifice, hence is functional and does not signify mitral stenosis.

COMMENTS

The most important auscultatory findings in ventricular septal defect are the systolic murmur, the splitting of the second heart sound and the apical third sound. Because there is a significant pressure gradient, and therefore blood flow across the defect throughout systole, a pansystolic murmur which buries the aortic second sound results. As long as there is a large shunt a long murmur should be produced.[2,3] The patient with proved pulmonary

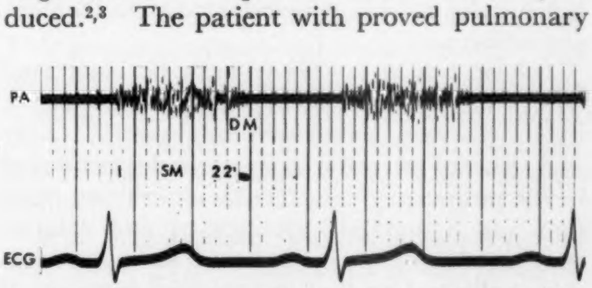

FIG. 8. Case 13. There is an early, short diastolic murmur in the pulmonary area. There was no pulmonary hypertension.

hypertension is the exception. This decreases the shunt and causes it to be bidirectional. The net effect, however, is to decrease the total flow across the defect and hence the murmur is softer and may not be pansystolic.[2] This was true in the three patients with the highest pulmonary artery and right ventricular pressures who proved to have the softest murmurs (Cases 40, 41 and 44), and in those with Eisenmenger's complex. Another factor is the size of the defect. In one patient who came to autopsy (Case 40), the defect was so large that it amounted to a single ventricle. In such cases murmurs may be insignificant.

Differential Diagnosis of the Systolic Murmur: The location of maximal intensity of the pansystolic murmur to the left of the sternum in the third to fourth intercostal space helps differentiate this murmur from that of *mitral regurgitation*, which is apical and radiates toward the axilla and left scapula. The murmur may be of sufficient intensity at the apical area to cause difficulty. However, in these cases the murmur will also be very loud at the tricuspid area and even to the right of the sternum which would be very unusual for mitral regurgitation. *Tricuspid regurgitation* would have to be differentiated on other clinical grounds as the murmur may be similar. Pulsations of the liver and the veins of the neck and an inspiratory increase in intensity of the murmur would favor the diagnosis of tricuspid regurgitation.

In *tetralogy of Fallot* the murmur is caused by the pulmonary stenosis.[4,5] Negligible flow occurs across the ventricular defect because of the equalization of right and left ventricular pressures. Therefore, in tetralogy of Fallot, the murmur is not pansystolic and ends distinctly before a loud single second sound which is due to aortic closure. In contrast, ventricular septal defect with pulmonary stenosis can be differentiated by the fact that the second heart sound is split and the pulmonary component diminished but usually audible or demonstrable on the phonocardiogram.

Isolated pulmonary stenosis may be associated with a murmur and thrill which is maximal in the third or even fourth intercostal space. However, careful attention to the second heart sound in the pulmonary area reveals an ejection murmur and a markedly diminished and delayed second pulmonary sound in contrast to a moderately split and normal or increased intensity of the pulmonary closure in ventricular septal defect.[6] If the differentiation by auscultation alone is still difficult, the phonocardiogram usually clarifies the situation. Clinical differentiation on the basis of the murmur alone is difficult because it may be so intense in pulmonary stenosis and ventricular septal defect that timing is difficult. We do not emphasize the shape of the registration of the murmur on the phonocardiogram as being of diagnostic value. In the majority of cases of ventricular septal defect the murmur was crescendo-decrescendo (Figs. 2, 6 and 7) and hence diamond-shaped. This may lead to an erroneous interpretation of pulmonary stenosis. Of greater importance is the timing of the murmur, being ejection in type and hence starting after the first sound and ending before the second sound in pulmonary stenosis[6,7] and being pansystolic in ventricular septal defect.[7–10]

Rarely the *aortic stenotic murmur* is maximal over the third or fourth left intercostal space and must be differentiated from ventricular septal defect. In the former, the murmur is ejection in type and ends before the aortic component of the second sound[11] whereas the murmur of ventricular septal defect extends up to and usually buries the aortic component. The carotid artery pulse tracing was normal in all our patients (Figs. 1 and 3) and is also helpful in differentiating aortic stenosis in which a slow ascent and delayed peak is characteristically demonstrated.[11]

Splitting of Pulmonary Second Sound: Normally, due to the increased stroke volume of the right ventricle on inspiration, there is splitting of the second sound due to a delay in the pulmonary closure.[12,13] The split in deep inspiration may normally reach as much as 0.08 second. However, on expiration the splitting narrows and the sound becomes single. Wide, fixed splitting due to delayed pulmonary closure occurs in such conditions as atrial septal defect and pulmonary stenosis,[6,14] which prolong the ejection time of the right ventricle. In delayed conduction in the right ventricle (complete right bundle branch block) there is also wide splitting of the second sound.[2] Early closure of the aortic valve may also be a factor in some cases of splitting of the second sound and probably is the mechanism that occurs in mitral regurgitation and possibly also in ventricular septal defect.[13,15] The early aortic closure in ventricular septal defect is probably also associated with some delay in pulmonary closure because of the large volume of blood ejected by the right ventricle. In our patients there was moderate splitting

TABLE II
Differential Points in Various Lesions Associated with a Ventricular Septal Defect

Lesion	Intensity of P_2	Splitting of P_2	Third Sound	Ejection Sound	Systolic Murmur	Diastolic Murmur
Ventricular septal defect with normal pressure	Normal or increased	Usually moderately split, occasionally not split	Common	Occasionally	Loud, pansystolic	Apical ventricular filling murmur occasionally heard
Ventricular septal defect with pulmonary hypertension	Increased	Usually narrowly split or single	Common	Common	Soft toned, may not be pansystolic	Apical ventricular filling murmur occasionally heard. Pulmonary diastolic murmur in over 50 per cent
Ventricular septal defect with infundibular pulmonary stenosis	Decreased	Widely split	Not common	Common	Pansystolic, loud	Apical ventricular filling murmur occasionally heard
Ventricular septal defect with aortic insufficiency	Normal or increased	Moderately split	Not common	Aortic ejection sound	Pansystolic, loud	Aortic diastolic
Eisenmenger's complex	Increased	Narrowly split or single	Not common	Common	Soft toned, not pansystolic	Pulmonary diastolic common
Tetralogy of Fallot	P_2 absent	Single second sound (aortic)	Not common	Common	Ejection type, may be loud	Diastolic murmur rarely observed

which varied somewhat with respiration, but usually the sound did not become single on expiration.

Prominent Third Sound and Diastolic Filling Murmur: A prominent third sound at the apex was a very common finding. Although it is also frequently heard in normal children, in our experience it is never so loud or prominent as that which occurs in ventricular septal defect. In addition, there is not uncommonly a low pitched filling murmur which follows the third sound and is caused by rapid flow of a larger than normal volume traversing the mitral valve[10,16,17] (Fig. 1). Although this murmur is at times similar in quality to the mid-diastolic rumble of mitral stenosis, it is functional in ventricular septal defect and the association of these two lesions must be exceedingly rare. It was not found in any of our patients who were operated on or who came to autopsy.

Pulmonary Regurgitation: An early, blowing diastolic murmur was caused by incompetence of the pulmonary valve.[17–19] It was heard in four of the seven patients with marked pulmonary hypertension (Fig. 8) but was recorded on the phonocardiogram in only two instances. This is in accord with our experience that very high frequency but low intensity murmurs are difficult to record on the phonocardiogram. It also emphasizes that phonocardiography cannot replace auscultation but merely supplements it.

Aortic Regurgitation: Ventricular septal defects with aortic regurgitation must be differentiated from patent ductus arteriosus and aortopulmonary septal defect. At times such differentiation is difficult, but there are aus-

cultatory differences. The murmur of patent ductus is not only continuous but is more machine or roaring in quality, and is heard well in the left infraclavicular area. It rises to a crescendo near the second sound so that at the pulmonary area the second sound is often not distinguishable.[20] In addition, there may be a distinct silent interval after the first heart sound before the systolic component starts. In ventricular septal defect with aortic insufficiency the murmur starts immediately with the first sound and is maximal in mid-systole. A distinct second sound (pulmonic) is usually heard over the pulmonary area and the diastolic murmur is of a distinctly different quality, blowing rather than roaring in character. The area of maximal intensity is lower and fades out toward the infraclavicular area.

A summary of the salient points in the differentiation of the various lesions associated with ventricular septal defect is listed in Table II. The systolic murmur and the intensity and splitting of the second sound are the most important clinical features which help to differentiate the various forms of ventricular septal defect.

Summary

1. Forty-four proved cases of ventricular septal defect have been reviewed from the auscultatory and phonocardiographic standpoint.

2. A loud, harsh pansystolic murmur, moderately split and normal to increased intensity of pulmonary closure, a third heart sound at the apex and occasionally a mid-diastolic ventricular filling murmur are the most characteristic observations. The systolic murmur is invariably associated with a thrill and is maximal in the third or fourth left intercostal space.

3. An aortic diastolic murmur was observed in three patients who had aortic insufficiency.

4. A widely split and decreased sound of pulmonary closure was noted in four patients with associated infundibular pulmonary stenosis.

5. Pulmonary hypertension caused a narrowly split or single second sound that was of increased intensity. The systolic murmur was softer and non-holosystolic in three of seven patients with pulmonary hypertension.

6. The differentiation between ventricular septal defect and other conditions associated with a similar harsh systolic murmur was briefly discussed.

References

1. Roger, H. L. Recherches clinique sur la communication congenitale des deux coeurs par inocclusion du septum interventricularie. *Bull. Acad. med. Paris*, 8: 1074, 1879.
2. Leatham, A. Auscultation of the heart. *Lancet*, 2: 703, 757, 1958.
3. Leatham, A. Auscultation of the heart. *Pediat. Clin. North America*, p. 839, November 1958.
4. Vogelpoel, L. and Schrire, V. The role of auscultation in the differentiation of Fallot's tetralogy from severe pulmonary stenosis with intact ventricular septum and right-to-left interatrial shunt. *Circulation*, 11: 714, 1955.
5. Vogelpoel, L., Schrire, V., Nellen, M. and Goetz, R. H. The differentiation of the tetralogy of Fallot from severe pulmonary stenosis with intact ventricular septum and right to left shunt. *Angiology*, 8: 213, 1957.
6. Leatham, A. and Weitzman, D. Auscultatory and phonocardiographic signs of pulmonary stenosis. *Brit. Heart J.*, 19: 303, 1957.
7. Kjellberg, S. R., Mannheimer, E., Rudhe, U. and Jonsson, B. Diagnosis of Congenital Heart Disease, Chicago, 1955. Year Book Publishers.
8. Friedberg, C. K. Diseases of the Heart, Philadelphia, 1956. W. B. Saunders Co.
9. Fyler, D. C., Rudolph, A. M., Wittenborg, M. H. and Nadas, A. S. Ventricular septal defects in infants and children. *Circulation*, 18: 833, 1958.
10. Wood, P. Congenital heart disease. *Brit. M. J.*, 2: 639, 653, 1950.
11. Wood, P. Aortic stenosis. *Am. J. Cardiol.*, 1: 553, 1958.
12. Leatham, A. and Towers, M. Splitting of the second heart sound in health. *Brit. Heart J.*, 13: 1575, 1951.
13. McKusick, V. A. Cardiovascular Sound in Health and Disease. Baltimore, 1958. Williams and Wilkins.
14. Leatham, A. and Gray, I. Auscultatory and phonocardiographic signs of atrial septal defect. *Brit. Heart J.*, 18: 193, 1956.
15. Perloff, J. K. and Harvey, W. P. Mechanisms of fixed splitting of the second heart sound. *Circulation*, 18: 998, 1959.
16. Wood, P., Magidson, O. and Wilson, P. A. O. Ventricular septal defect with a note on acyanotic Fallot's tetralogy. *Brit. Heart J.*, 16: 387, 1954.
17. Nadas, A. S. Pediatric Cardiology. Philadelphia, 1957. W. B. Saunders Co.
18. Agustsson, M. H., DuShane, J. W. and Swan, J. C. Ventricular septal defect in infancy and childhood. Clinical and physiologic study of 19 cases. *Pediatrics*, 20: 848, 1957.
19. Blount, S. H., Jr., Mueller, H. and McCord, M. C. Ventricular septal defect. Clinical and hemodynamic patterns. *Am. J. Med.*, 18: 871, 1955.
20. Neill, C. and Mounsey, P. Auscultation in patent ductus arteriosus, with a description of two fistulae simulating patent ductus. *Brit. Heart J.*, 20: 61, 1958.

The Electrocardiogram and Vectorcardiogram in Ventricular Septal Defect*

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ELECTROCARDIOGRAPHY (including vectorcardiography) constitutes one of the most valuable diagnostic procedures in the study of patients with ventricular septal defects. Correlation of the electrocardiogram with the physical and roentgenographic findings and the catheterization data provides valuable information concerning the severity and progression of the lesion and the presence of right or left ventricular hypertrophy (overloading) or combined hypertrophy. Frequently, certain distinctive findings in the electrocardiogram and vectorcardiogram help to differentiate ventricular septal defect from other acyanotic congenital lesions such as pulmonic stenosis, atrial septal defect and aortic stenosis.

The electrocardiographic and vectorcardiographic findings in ventricular septal defect have been reported in considerable detail in recent papers.[1-6] These studies have helped to elucidate the criteria for predominant right ventricular hypertrophy in the presence of left ventricular hypertrophy, and predominant left ventricular hypertrophy in the presence of right ventricular hypertrophy. This is of great importance since most ventricular septal defects, at some time in their development, produce combined left and right ventricular overloading and hypertrophy.

In general, the effect of a ventricular septal defect on the electrocardiogram will depend on the size of the defect, the magnitude of the left-to-right shunt flow, the relative degree of overloading and enlargement of the two ventricles, the pulmonary vascular resistance and the presence or absence of pulmonary hypertension. As emphasized in the first paper of this symposium[7] which summarized the physiology and life history of ventricular septal defect, this is a dynamic and progressively changing condition, with varying sizes of interventricular shunts and variable degrees of right and left ventricular overloading and "strain." Therefore, a variety of electrocardiographic patterns are seen in different patients depending on the severity of the lesion, and in the same patient in different periods of life as the hemodynamic changes progress.

DIAGNOSIS OF BIVENTRICULAR HYPERTROPHY

Most patients with a moderate to severe ventricular septal defect have enlargement or "overloading" of both ventricles as a result of the left-to-right shunt and the increased flow through the pulmonary circulation and left-sided cardiac chambers. It would be wise, therefore, to summarize the known diagnostic criteria for diagnosing biventricular hypertrophy or "overloading" in the electrocardiogram and vectorcardiogram.[6] The diagnosis of biventricular hypertrophy is quite difficult since the criteria are less clear-cut than those for pure left or pure right ventricular hypertrophy. The criteria presented in some previous studies have been derived predominantly from adult patients with acquired or congenital heart disease and may not be applicable to infants and young children with ventricular septal defects. In the latter age group, in which physiologic preponderance of the right ventricle is present normally, it may be exceedingly difficult to detect mild to moderate degrees of left ventricular hypertrophy, especially in the presence of right ventricular hypertrophy. Conversely, the signs of early right ventricular hypertrophy in adults may be masked in the presence of left ventricular hypertrophy. In other words, if one ventricle is hypertrophied out of proportion to the other in combined ventricular hypertrophy, the predominant ventricle will dominate the electrical forces and the electrocardiogram will reflect hypertrophy of

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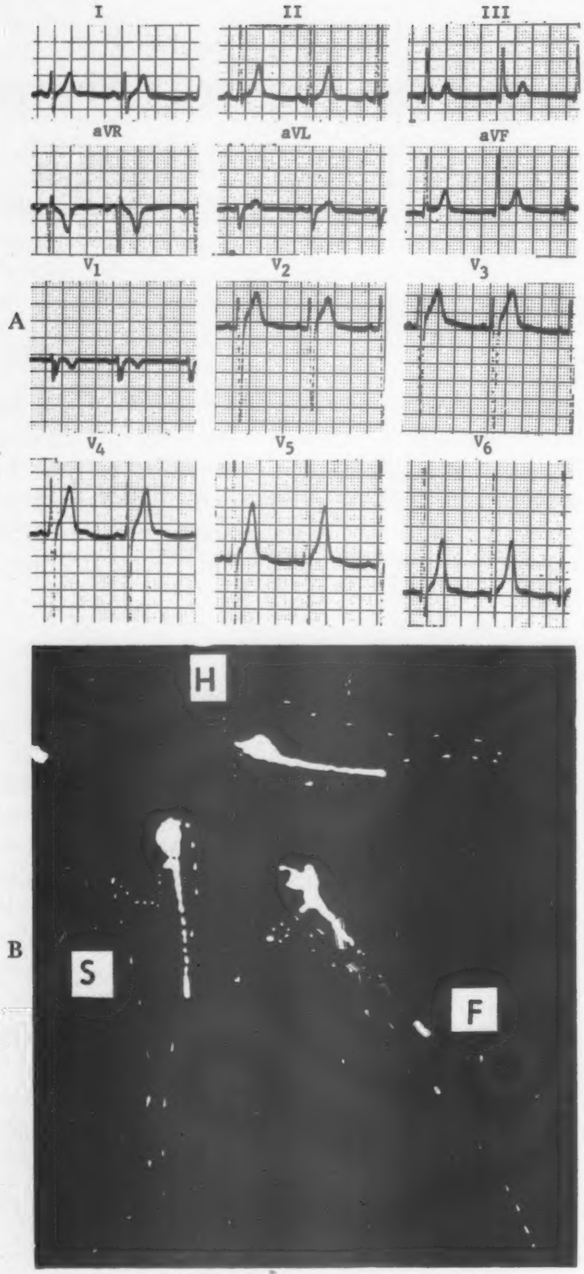


FIG. 1. Small ventricular septal defect in a fifteen year old boy. Catheterization findings were: right ventricular pressure 30/5 mm. Hg; pulmonary artery pressure 25/6 mm. Hg; and right ventricular oxygen step-up 1 vol. per cent. The electrocardiogram (A) and vectorcardiogram (B) are within the range of normal. Note the tall peaked T in lead V_6 which has been attributed to left ventricular "diastolic overloading."

one ventricle alone. The vectorcardiogram may be of greater aid than the electrocardiogram in establishing the presence of combined hypertrophy. The following electrocardiographic and vectorcardiographic criteria have been found to be useful in evaluating biventricular hypertrophy in patients with a ventricular septal defect.

ELECTROCARDIOGRAPHIC CRITERIA FOR DIAGNOSING RIGHT VENTRICULAR HYPERTROPHY (IN COMBINED HYPERTROPHY)[6, 8–14]

(1) A tall R or R′ in lead V_1 exceeding 7 mm. This attains more significance when the R/S ratio in lead V_1 is greater than 1 in patients over five to six years of age. In younger patients the ratio should be larger since it may approach 5 in normal infants.[15]

(2) Intrinsicoid deflection in lead V_1 exceeding 0.03 second.

(3) Deep S waves exceeding 7 mm. in leads V_5 and V_6. Occasionally, the R is so small and S so deep that the R/S ratio in these leads is less than 1.

(4) Tall R exceeding 5 mm. in lead aVR, or a Q/R or S/R ratio less than 1 in this lead.

(5) Right axis deviation in the standard extremity leads. The mean axis generally lies between +45 and +135 degrees and there is a prominent S in lead I. Frequently, the final QRS vectors in the frontal plane point upward and to the right (terminal axis above −150 degrees), producing an S wave in leads II and III as well as in lead I (biphasic QRS in extremity leads).

The first of these criteria (tall R and R/S ratio exceeding 1 in lead V_1) is the most important, being found alone or combined with the other criteria in almost all cases of biventricular hypertrophy. The other criteria occur in one-third to one-half of the cases. The configuration of the QRS in lead V_1 varies; it may be Rs, rSR, rSRs or qR. These patterns have been attributed to "diastolic overloading" of the right ventricle with hypertrophy of the outflow tract and crista portion. In a few cases there may be a tall broad R with slurring or notching of the upstroke (rR) with or without a small S. This has been attributed to "systolic overloading" of the right ventricle with hypertrophy of the free wall and of the septal and paraseptal areas.[5]

ELECTROCARDIOGRAPHIC CRITERIA FOR LEFT VENTRICULAR HYPERTROPHY (IN COMBINED HYPERTROPHY)[4,8,12,16,17]

(1) Left axis deviation in the standard extremity leads with an electrical axis of zero degrees or less. Generally, the left axis deviation (S waves in leads II and III) is acompanied by a small S in lead I.

(2) R wave in lead aVL greater than 15 mm. (this generally occurs with left axis deviation).

(3) R waves in leads V_5 or V_6 of 34 mm. or more, or greater than 25 mm. if accompanied by a small S wave. Often a prominent Q precedes the R (qR or qRs pattern).

(4) Intrinsicoid deflection in leads V_5 or V_6 greater than 0.05 second. Such delay is uncommon but is more frequent if the value for the upper limit of normal is considered to be 0.04 rather than 0.05 second (particularly in infants). In a recent study[4] in which this value was used, evidence of left ventricular hypertrophy was observed in over three-fourths of patients.

(5) Depression of RS-T segment or lowering of T wave in leads V_5 or V_6 in the presence of an R over 25 mm. This has been attributed to "systolic overloading" of the left ventricle.[18] More frequently the T wave in leads V_5 or V_6 may be tall and peaked, suggesting "diastolic overloading" of the left ventricle.[18] In a recent study, this finding was observed in 60 per cent of patients.[4]

The diagnosis of left ventricular hypertrophy is usually definite when two or more of the aforementioned criteria are present. When signs of right ventricular hypertrophy are also observed the diagnosis of biventricular hypertrophy should be considered. The diagnosis of left ventricular hypertrophy is questionable when a tall R in leads V_5 or V_6 is the only evidence but in many cases of ventricular septal defect it may be the only electrocardiographic finding to arouse suspicion of left "ventricular overloading."

Biphasic QRS: Another characteristic finding suggesting biventricular hypertrophy in ventricular septal defect is a large biphasic QRS in the precordial leads (V_2 to V_6) as well as equiphasic complexes in the extremity leads.[19] These are generally observed in infancy and early childhood (one-fourth of cases) and are less common in older patients.

VECTORCARDIOGRAPHIC CRITERIA FOR DIAGNOSING COMBINED VENTRICULAR HYPERTROPHY[6,20–22]

(1) In most patients the QRS loop in the horizontal and sagittal planes is displaced anteriorly as seen in right ventricular hypertrophy. In nearly all of these patients there will be other atypical changes in orientation or configuration which will suggest associated left ventricular hypertrophy.

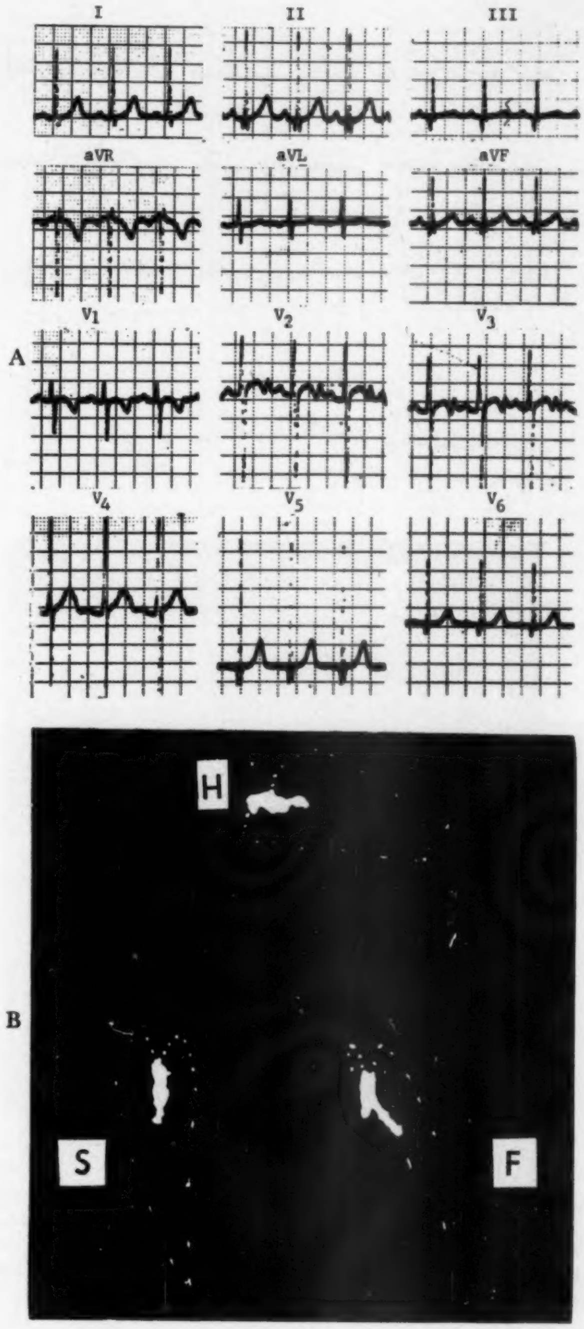
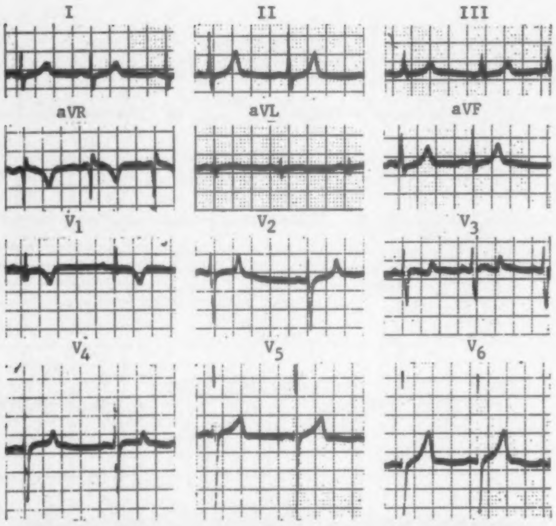


FIG. 2. Small ventricular septal defect in a five year old girl. Catheterization findings were: right ventricular pressure 34/0 mm. Hg; pulmonary artery pressure 30/12 mm. Hg; and right ventricular oxygen step-up 1.0 vol. per cent. The electrocardiogram (A) is in the range of normal. However, the prominent Q and tall R in lead V_6, although not abnormal, are suggestive of early left ventricular preponderance or "overloading." The vectorcardiogram (B) is normal in all projections.

(2) In about one-third of patients the QRS loop in the horizontal plane initially is oriented anteriorly and to the right. It then proceeds to the left and is inscribed counterclockwise as



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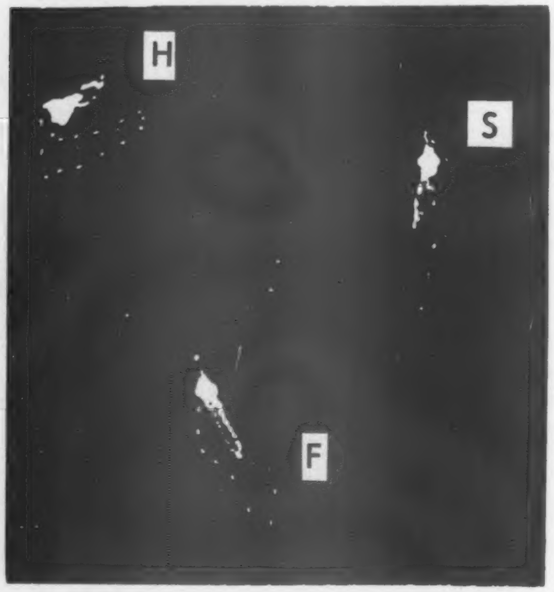


FIG. 3. Moderate-sized ventricular septal defect in a five year old boy. Catheterization findings were: right ventricular pressure 38/0 mm. Hg; pulmonary artery pressure 35/5 mm. Hg; and right ventricular oxygen step-up 1.5 vol. per cent. Surgical findings were a 1.5 cm. ventricular septal defect, closed successfully. The electrocardiogram (A) shows biventricular hypertrophy with preponderance of the right ventricle; small S_1, S_2, S_3, small R in lead aVR and S in lead aVF; QRs pattern and deeply inverted T in lead V_1; persistent deep S waves in leads V_2 to V_6 with biphasic QRS complexes. The vectorcardiogram (B) shows the QRS loop displaced anteriorly in the horizontal plane (H) and inscribed clockwise, indicative of right ventricular hypertrophy. In the sagittal plane (S) the QRS loop is oriented anteriorly and downward, and in the frontal plane (F) it is oriented downward (+75 degrees) and inscribed counterclockwise. The latter suggests associated left ventricular hypertrophy.

in the normal state instead of clockwise as in pure right ventricular hypertrophy. This suggests associated left ventricular hypertrophy.

(3) In another one-third of patients, there is a figure-of-eight configuration of the QRS loop in the horizontal plane, with the terminal limb inscribed clockwise. This may occur in pure right ventricular hypertrophy but in biventricular hypertrophy the loop in the frontal plane is displaced to the left (producing left axis deviation) and is inscribed counterclockwise, suggesting associated left ventricular hypertrophy.

(4) In an occasional case of biventricular hypertrophy, there is the classic anterior, clockwise QRS loop in the horizontal plane, but as in (3) just mentioned, the loop in the frontal plane points to the left and is rotated counterclockwise. This, too, suggests associated left ventricular hypertrophy.

(5) In young infants (below six months of age) a large defect may be associated with an anteriorly displaced QRS loop in the horizontal plane which, although suggestive of right ventricular hypertrophy, may be in the range of normal for this age group.

Correlation of Electrocardiogram and Vectorcardiogram with Other Clinical Findings

A great deal of diagnostic help can be derived from the electrocardiogram and vectorcardiogram in patients with ventricular septal defect, particularly when the findings are correlated with other clinical and hemodynamic data. From this standpoint, several types of cardiographic patterns may be observed.

Normal Electrocardiogram and Vectorcardiogram: Normal tracings are recorded in about one-third of children and adults with ventricular septal defect (Figs. 1 and 2). The presence of a normal electrocardiogram and vectorcardiogram generally indicates that the defect and left-to-right shunt are small.[2,3,6,21] In such patients, the heart is usually normal in size or only slightly enlarged and the vascular markings of the lung are normal or only slightly increased. Cardiac catheterization reveals a small shunt flow with normal right ventricular and pulmonary artery pressures.

In infants, however, particularly those below the age of seven months, a normal electrocardiogram and vectorcardiogram may be observed even in the presence of a moderate to large defect.[6] This may be related to the difficulty in interpretation of the tracings in young infants. The differentiation of physiologic from pathologic degrees of right ventricular preponderance may be impossible in this

age group, and as stated before, the recognition of associated left ventricular hypertrophy or strain in such records may be impossible. Even in older infants or children a normal electrocardiogram and vectorcardiogram may sometimes be recorded in the presence of combined ventricular hypertrophy. The balance of forces may not be sufficiently altered and may remain in the normal range when both ventricles are symmetrically enlarged or when left ventricular hypertrophy counterbalances the physiologic right ventricular preponderance of infancy.

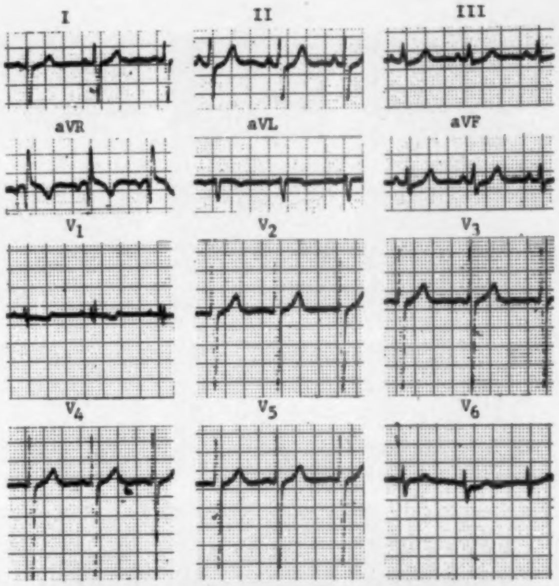
Even when the electrocardiogram appears to be in the range of normal, there may be certain changes suggestive of a mild degree of left ventricular preponderance or overloading such as a tall R or tall peaked T (Fig. 1A) or prominent Q in leads V_5 and V_6 (Fig. 2A).

Right Bundle Branch Block: This conduction defect is not so frequent in ventricular septal defect as in other congenital lesions, but may occur occasionally as a result of involvement of the bundle branch by the defect.[2,3] It is generally of the incomplete type. Its presence gives no indication as to the size and severity of the defect, since it may occur in small defects as well as in large ones. Also, in contrast to the association of "incomplete right bundle branch block" with right ventricular hypertrophy in atrial septal defect, it may occur in mild ventricular septal defects in the absence of right ventricular hypertrophy.

Combined Ventricular Hypertrophy: Combined ventricular hypertrophy can be diagnosed from either the electrocardiogram or vectorcardiogram or both in about half the patients with ventricular septal defect (Figs. 3 and 4). The configuration will vary in different patients depending upon the size of the defect, the magnitude of the shunt flow and the degree of pulmonary hypertension.[2,3,6,22] With rare exception the pattern of combined hypertrophy is observed in patients who have a moderate to severe defect with a large left-to-right shunt, and mild to moderate increase in pulmonary artery pressure. In other words, there is a "high flow and low or high pressure" defect with overloading and enlargement of both ventricles. The right ventricular and pulmonary artery systolic pressures may occasionally be normal despite the large shunt, but generally they range between 40 and 90 mm. Hg; occasionally they may rise to 105 to 110 mm. Hg.

In the latter patients with considerable right ventricular and pulmonary hypertension the electrocardiogram and vectorcardiogram usually show significant degrees of right ventricular hypertrophy which is more clearly delineated

A



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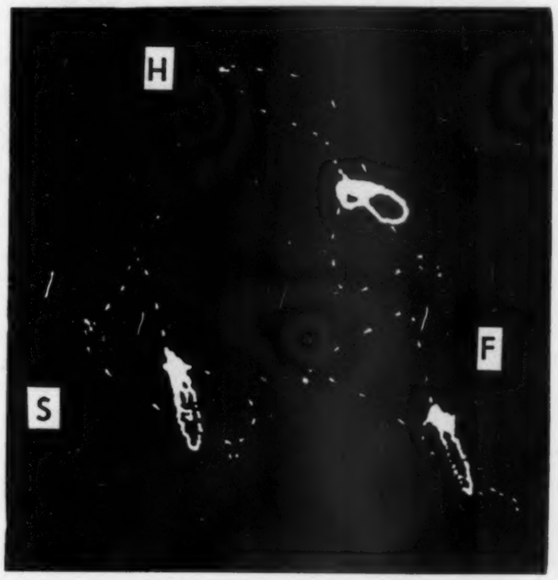

Fig. 4. Large ventricular septal defect with large left-to-right shunt and pulmonary hypertension in a ten year old girl. Catheterization findings were: right ventricular pressure 106/6 mm. Hg; pulmonary artery pressure 102/52 mm. Hg; and right ventricular oxygen step-up 4 vol. per cent. The electrocardiogram (A) shows biventricular hypertrophy with predominent right ventricular "overloading": right axis deviation with deep S_1, S_2 and small S_3, tall R in lead aVR, prominent S in lead aVF, RSR in lead V_1 and biphasic RS complexes in leads V_2 to V_6. The vectorcardiogram (B) confirms the presence of biventricular hypertrophy: in the horizontal plane, the QRS loop is inscribed counterclockwise, initially anteriorly and terminally posteriorly; in the sagittal and frontal planes, the QRS loop is superiorly oriented to the right, first anteriorly and then posteriorly.

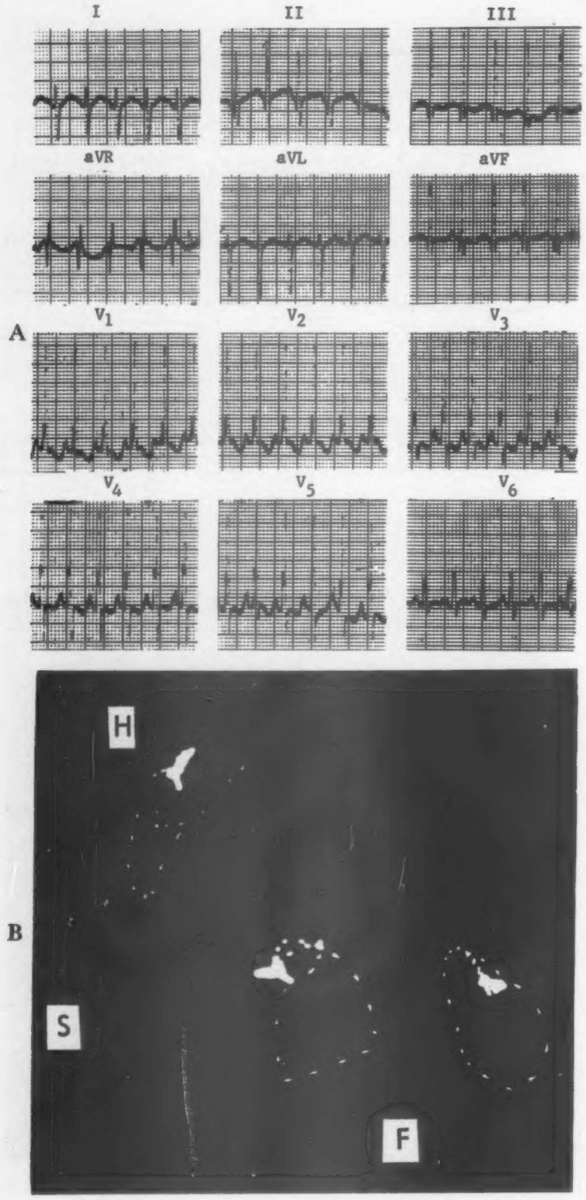

Fig. 5. Large ventricular septal defect with large left-to-right shunt and infundibular stenosis (hypertrophy of the outflow tract) in a five year old boy. Catheterization findings were: right ventricular pressure 80/5 mm. Hg; pulmonary artery pressure 38/15 mm. Hg; and right ventricular oxygen step-up 3.3 vol. per cent. The electrocardiogram (A) shows marked right ventricular hypertrophy; right axis deviation, R in lead aVR, tall rR′ and inverted T in leads V_1 to V_3 and persistent S in leads V_5 and V_6. The vectorcardiogram (B) confirms the presence of right ventricular hypertrophy: QRS loop displaced anteriorly and to the right and inscribed clockwise in the horizontal plane (H), displaced anteriorly in the sagittal plane (S) and to the right in the frontal plane (F) where it is also inscribed clockwise.

than the signs of left ventricular hypertrophy or overloading.[22] Occasionally the pattern may be that of pure right ventricular hypertrophy.

Pure Right Ventricular Hypertrophy: Electrocardiographic and vectorcardiographic patterns of "pure" right ventricular hypertrophy are uncommon in ventricular septal defect,[2,3,6] being observed in less than 15 per cent of cases (Fig. 5). The presence of signs of right ventricular hypertrophy without evidence of left ventricular overloading should suggest (1) marked pulmonary hypertension or (2) associated infundibular stenosis of the right ventricle due to hypertrophy of the outflow tract and crista region.[5,23] As previously stated, increasing evidence of right ventricular hypertrophy and the disappearance of signs of left ventricular hypertrophy point to increasing right ventricular hypertension as a result of one of these two factors, namely, pulmonary hypertension or infundibular stenosis due to hypertrophy of the outflow tract.[7,24] In such cases, although the size of the defect at operation or autopsy is generally large (2.5 cm. or greater), the marked right ventricular systolic hypertension results in equalization of pressures in the two ventricles with decrease in the left-to-right shunt flow. Further increases in right ventricular pressure exceeding the left will result in reversal of flow during certain periods of the cardiac cycle and cyanosis. Such cases fall into the group of Eisenmenger's complex. In other cases, cardiac catheterization may demonstrate the presence of an infundibular chamber with high systolic pressure in the inflow tract of the right ventricle and normal pressure in the infundibular chamber (outflow tract) and pulmonary artery.

Pure Left Ventricular Hypertrophy: Although most patients with moderate or large ventricular septal defects show signs of overloading of the left as well as of the right ventricle, electrocardiographic and vectorcardiographic signs of pure left ventricular hypertrophy are rare.[2,3,6] An occasional patient will show very tall R waves, delayed intrinsicoid deflection and peaked or inverted T waves in leads V_5 and V_6, or a marked degree of left axis deviation (0 to -30 degrees) without signs of right ventricular overloading. Such a pattern generally indicates a large defect with a large left-to-right shunt.[24] A similar pattern may be observed in patients with a large patent ductus arteriosus. Although the presence of associated aortic insufficiency in ventricular septal defect may accentuate the findings of left ventricular hypertrophy, the tracings may remain normal or show biventricular hypertrophy.[25,26]

As already mentioned, patients whose electro-

cardiographic and vectorcardiographic tracings fall into the normal range may show early signs of left ventricular "overloading" or preponderance which are suggestive but not diagnostic. These include high voltage of the R or tall peaked T waves or prominent Q waves in the left precordial leads (Figs. 1 and 2).

Other Electrocardiographic Features: Disorders of rhythm are not common in ventricular septal defect. An occasional patient may show nodal rhythm or ventricular extrasystoles. The P-R interval has been observed to be at the upper limit of normal or slightly prolonged in over half the cases. Rarely, complete A-V block may be present from birth.

Electrocardiographic evidence of right or left atrial enlargement is not uncommon. Right atrial enlargement (tall or peaked P wave in lead V_1) has been observed in one-fourth of the patients and left atrial enlargement (broad, prominent P waves in leads I and V_5 or V_6) in one-third.[6] In a few patients evidence of combined atrial hypertrophy is present ("P congenitale").[27]

Differential Diagnosis

It is evident from the previous discussion that the electrocardiogram and vectorcardiogram in ventricular septal defect may be normal or show variable degrees of right or left ventricular hypertrophy or both. Differentiation from other congenital lesions may be difficult on the basis of the cardiographic patterns alone, but correlation with the other clinical findings will generally allow such differentiation in the majority of cases. With the aid of the electrocardiogram and vectorcardiogram the individual case of congenital heart disease can be generally classified into a broad category of one or two lesions and not infrequently a more specific diagnosis can be made.

Lesions Associated with Normal Tracings: In addition to a mild ventricular septal defect the following common congenital lesions should be considered in the presence of normal electrocardiographic and vectorcardiographic tracings: patent ductus arteriosus and occasionally mild coarctation of the aorta and aortic stenosis. These can generally be excluded easily by the other clinical findings associated with each of these lesions (character and transmission of the murmur, presence of a to-and-fro murmur, difference in blood pressure in upper and lower extremities, roentgenographic findings, etc.). A normal electrocardiographic or vectorcardiographic tracing generally excludes atrial septal defect and pulmonic stenosis.

Lesions Producing Left Ventricular Hypertrophy: Left ventricular preponderance may be observed in patent ductus arteriosus, aortic stenosis, coarctation of the aorta and tricuspid atresia. In this group, as in the first group with normal tracings, differentiation with the aid of the other clinical findings is usually simple. Pure left ventricular hypertrophy in ventricular septal defect is uncommon but generally occurs with very large left-to-right shunts. Roentgenographic and physical examinations will help to exclude the cases of aortic stenosis and coarctation. However, differentiation from patent ductus will be difficult unless the characteristic murmur is audible, since both lesions may produce a similar roentgenographic appearance with enlargement of the pulmonary artery and its branches and increased pulmonary vasculature as a result of the increased pulmonary blood flow.

Lesions Producing Right Ventricular Hypertrophy: When signs of pure right ventricular hypertrophy are present without left-sided hypertrophy, one must consider atrial septal defect, pulmonary stenosis, tetralogy of Fallot, transposition of the great vessels, Eisenmenger's syndrome and idiopathic pulmonary hypertension. Since the pattern of pure right ventricular hypertrophy is rare in ventricular septal defect except in cases of severe pulmonary hypertension and balanced or reversed shunt (Eisenmenger's complex) or infundibular stenosis due to hypertrophy of the outflow tract, it is important to exclude the aforementioned lesions first before considering the diagnosis of ventricular septal defect. Cardiac catheterization is generally necessary to clarify the diagnosis.

Lesions Producing Biventricular Hypertrophy: When signs of combined ventricular hypertrophy are present one must differentiate between the lesions producing a left-to-right shunt. The most frequent differential diagnosis is that between ventricular septal defect and patent ductus arteriosus. This is particularly important during infancy when the murmurs of patent ductus may be atypical. The diastolic murmur may be faint and may be blowing rather than machinery in character and maximal at the apex or lower sternal area rather than in the pulmonic area. Other possible causes of left-to-right shunt associated with biventricular hypertrophy are aortopulmonary fistula and persistent A-V canal. In the latter

lesion, a characteristic finding is the superior orientation of the QRS vector loop in the frontal and sagittal planes, producing left axis deviation or deep S waves in the three standard leads. However, this has been observed occasionally in pure ventricular septal defect without associated atrial septal or endocardial cushion defects. The most common cause for an intracardiac left-to-right shunt, namely, atrial septal defect, can generally be excluded when any sign of left ventricular overloading or hypertrophy is present.

It is in this group of patients with biventricular hypertrophy that the vectorcardiogram demonstrates its superiority to the conventional electrocardiogram. Not infrequently the latter suggests isolated right ventricular hypertrophy because of the presence of a tall R in lead V_1 and absence of other conclusive signs of left ventricular hypertrophy. In such a patient, the vectorcardiogram in the horizontal plane may show a QRS loop which is initially oriented anteriorly and to the right, corresponding to the tall R in lead V_1. However, the continuation of the loop is inscribed counterclockwise, as observed in the normal subject or in the patient with left ventricular hypertrophy, rather than clockwise, as expected in right ventricular hypertrophy. Furthermore, the frontal plane QRS loop may also be inscribed counterclockwise rather than clockwise. Such a vectorcardiogram would indicate the presence of biventricular hypertrophy as seen in ventricular septal defect or patent ductus arteriosus, rather than the diagnosis of atrial septal defect or pulmonic stenosis which would be considered if only the conventional electrocardiogram were available.

Summary

1. The electrocardiogram and vectorcardiogram in ventricular septal defect may be normal or show variable degrees of left or right ventricular hypertrophy or of combined ventricular hypertrophy. The changes depend on the size of the defect, the magnitude of the left-to-right shunt, the severity of the pulmonary hypertension and infundibular hypertrophy of the right ventricle.

2. A normal electrocardiogram and vectorcardiogram generally indicate a small defect and a small left-to-right shunt.

3. Left ventricular overloading or hypertrophy indicates a moderate-sized to large left-to-right shunt.

4. Combined ventricular hypertrophy is observed in moderate to severe defects with large left-to-right shunts, with or without pulmonary hypertension.

5. Electrocardiographic and vectorcardiographic signs of pure right ventricular hypertrophy are uncommon and when present indicate either severe pulmonary hypertension or infundibular stenosis of the right ventricle due to hypertrophy of the crista. Increasing signs of right ventricular hypertrophy suggest increasing right ventricular hypertension due to one of these two factors.

6. The electrocardiogram and vectorcardiogram can aid in the differentiation of ventricular septal defect from atrial septal defect, pulmonary stenosis, patent ductus arteriosus, common A-V canal, tetralogy of Fallot and Eisenmenger's complex.

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References

1. Marsico, F., Peñaloza, D., Tranchesi, J., Limon, R. and Sodi-Pallares, D. The electrocardiogram in ventricular septal defect. Scalar and vectorial analysis of 32 cases. *Am. Heart J.*, 49: 188, 1955.
2. Blount, S. G., Mueller, H. and McCord, M. C. Ventricular septal defect. *Am. J. Med.*, 18: 871, 1955.
3. Kjellberg, S., Mannheimer, E., Rudhe, U. and Jonsson, B. Diagnosis of Congenital Heart Disease, 2nd ed. Chicago, 1958. Year Book Publishers.
4. Toscano-Barboza, E. and DuShane, J. W. Ventricular septal defect. Correlation of electrocardiographic and hemodynamic findings in 60 proved cases. *Am. J. Cardiol.*, 3: 721, 1959.
5. Warren, J. E. and Jannicelli, A. L. Reassessment of electrocardiographic findings in isolated interventricular septal defect. *Am. J. Cardiol.*, 3: 733, 1959.
6. Beregovich, J., Bleifer, S., Donoso, E. and Grishman, A. Vectorcardiogram and electrocardiogram in ventricular septal defect, with special reference to the diagnosis of combined ventricular hypertrophy. *Brit. Heart J.* (In press.)
7. Dammann, J. F., Thompson, W. M., Jr., Sosa, O. and Christlieb, I. The anatomy, physiology and natural history of simple ventricular septal defect. *Am. J. Cardiol.*, 5: 136, 1960.
8. Sodi-Pallares, D., Parás, O., Cabrera, C. E. and Mendoza, F. La deflexion intrinsica en casos normales y hipertrofias ventriculares. *Arch. Inst. cardiol. México*, 16: 397, 1946.
9. Sokolow, M. and Lyons, T. P. The ventricular

complex in right ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am. Heart J.*, 38: 273, 1949.
10. Donzelot, E., Metianu, C. and Durand, M. Les hypertrophies ventriculaires droites dans les cardiopathies congenitales (essai de classification physiopathologique des modifications electrocardiographiques). *Arch. mal coeur*, 45: 97, 1952.
11. Goodwin, J. F.: Electrocardiogram in normal children and in children with right ventricular hypertrophy. *Brit. Heart J.*, 14: 173, 1952.
12. Braunwald, E., Donoso, E., Sapin, S. O. and Grishman, A. A study of the electrocardiogram and vectorcardiogram in congenital heart disease. I. Electrocardiographic criteria for ventricular hypertrophy. *Am. Heart J.*, 50: 591, 1955.
13. Milnor, W. R. Electrocardiogram and vectorcardiogram in right ventricular hypertrophy and right bundle branch block. *Circulation*, 16: 348, 1957.
14. Holman, A. Electrocardiographic diagnosis of right ventricular hypertrophy in infancy and childhood. *Brit. Heart J.*, 20: 129, 1958.
15. Ziegler, R. F. Electrocardiographic Studies in Normal Infants and Children. Springfield, Ill., 1951. Charles C Thomas.
16. Sokolow, M. and Lyon, T. P. Ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am. Heart J.*, 37: 161, 1949.
17. Rosenman, R. H., Krause, S., Hwang, W. and Katz, L. N. The electrocardiographic diagnosis of combined left and right ventricular strain. *Am. Heart J.*, 40: 453, 1950.
18. Cabrera, C. E. and Monroy, J. R. Systolic and diastolic overloading of the heart. I. Physiological and clinical data. II. Electrocardiographic data. *Am. Heart J.*, 43: 661, 669, 1952.
19. Katz, L. N. and Wachtel, H. Diphasic QRS type of electrocardiogram in congenital heart disease. *Am. Heart J.*, 13: 202, 1937.
20. Donoso, E., Sapin, S. O., Braunwald, E. and Grishman, A. A study of the electrocardiogram and vectorcardiogram in congenital heart disease. II. Vectorcardiographic criteria in ventricular hypertrophy. *Am. Heart J.*, 50: 674, 1955.
21. Braunwald, E., Sapin, S. O., Donoso, E. and Grishman, A. A study of the electrocardiogram and vectorcardiogram in congenital heart disease. III. Electrocardiographic and vectorcardiographic findings in various abnormalities. *Am. Heart J.*, 50: 823, 1955.
22. Weiner, S. M., Levinson, D. C. and Elek, S. R. Ventricular septal defect and pulmonary hypertension. Electrocardiographic, spatial vectorcardiographic and cardiac catheterization findings. *Am. J. Cardiol.*, 1: 191, 1958.
23. Wood, P., Magidson, O. and Wilson, P. A. O. Ventricular septal defect with a note on acyanotic Fallot's tetralogy. *Brit. Heart J.*, 16: 387, 1954.
24. Fyler, D. C., Rudolph, A. M., Wittenberg, M. H. and Nadas, A. S. Ventricular septal defect in infants and children. A correlation of clinical, physiological, and autopsy data. *Circulation*, 18: 833, 1958.
25. Scott, R. C., McGuire, J., Kaplan, S., Fowler, N. O., Green, R. S., Gordon, L. Z., Shabetar, R. and Davolos, D. D. The syndrome of ventricular septal defect with aortic insufficiency. *Am. J. Cardiol.*, 2: 530, 1958.
26. Denton, C. and Pappas, E. G. Ventricular septal defect with aortic insufficiency. *Am. J. Cardiol.*, 2: 554, 1958.
27. Zuckermann, R., Guzmán de la Garza, C., Cisneros, F. and Medrano, G. A. El electrocardiograma en 21 tipos diferentes de cardiopatías congenitas. *Arch. Inst. cardiol. México*, 22: 550, 1952.

The Roentgenographic Spectrum in Interventricular Septal Defect*

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THE roentgenologic features in ventricular septal defects have been described extensively, but only in recent years has it been possible to delineate the special features and individual variations. Credit for this better understanding is due to the development of physiological data derived from cardiac catheterization and angiocardiography, from the application of such data to open heart surgery, and finally from derivative analyses of postmortem material.

In a hospital population correlative physiologic and anatomic data in patients with congenital heart disease are obtained mainly in a highly selected group of patients, hospitalized for potentially correctible surgery or for the care of advanced serious illness. Less selected material is obtainable from cardiac clinics where referrals for evaluation of murmurs make for a more adequate estimate of the true incidence and the relative weight of benign versus more severe defects.

As it is virtually impossible to screen all such cases by cardiac catheterization and angiocardiography, the cases presented in this series reflect the relatively more advanced or the severe situation rather than the milder or earlier phase of the disease process. Nevertheless, even in our own hospital material, the range of roentgenographic data is broad, varying from the apparently normal to that of marked cardiac enlargement and pulmonary congestion. Such correlative data as have been obtained serve to enhance the diagnostic value of the roentgenographic findings.

CASE MATERIAL

The physiologic data obtained in fifty consecutive cases of proved ventricular septal defects were therefore reviewed and correlated with the roentgenologic findings. This series does not include any patients with associated defects such as aortic or pulmonic stenosis, anatomical over-riding of the aorta, patent ductus arteriosus or coarctation. Half of this group of fifty patients came to surgery or to autopsy so that information as to the size and location of the defect and the microscopic appearance of a biopsy specimen of the lungs was obtained. The anatomic classification of ventricular septal defects is that of Edwards and his collaborators.[1,2]

Cardiac catheterization had been performed in the usual manner. An oxygen step-up of 5 per cent or more from atrial to ventricular sampling was considered indicative of a left-to-right shunt at the ventricular level. The degree of pulmonary hypertension was classified as severe if the ratio of pulmonary artery systolic pressure to femoral artery systolic pressure was 70 per cent or more; moderate if the range was between 40 and 70 per cent; and mild if 25 to 40 per cent. Pulmonic flow was obtained from the formula:[3]

$$QPA = QS \; \frac{CRV - CRA}{CLV - CRV}$$

in which QPA = blood flow in pulmonary artery; QS = systemic blood flow; CRV = oxygen concentration in the right ventricle; CRA = oxygen concentration in the right atrium; and CLV = oxygen concentration in the left ventricle.

If, in this formula, systemic flow is considered to be 100 per cent, then the pulmonic flow can be expressed as the percentage increase over the systemic flow.

SITE AND SIZE OF DEFECTS

Anatomically, defects in the ventricular septum as noted at operation or at autopsy, as seen from the right ventricular side, may involve either the outflow or the inflow tract. The outflow tract of the septal wall of the right ventricle lies between the pulmonary valve above and the nearest portion of the tricuspid valve below. The inflow tract is located posterior and caudal to the outflow tract (Fig. 1).

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The most common site of the defect is in the *ventricular outflow tract* below the crista supraventricularis. As Edwards has pointed out, although these are usually classified as "membranous" ventricular septal defects, they actually involve a larger zone of muscular tissue adjacent to the membranous septum. The size of the defect is determined primarily by the extent of the defect in this muscular portion. The less common type of ventricular outflow tract defect involves the area superior to the crista supraventricularis and is thus even closer in its relationship to the pulmonary valve.

Two types of ventricular septal defects are recognized in the *inflow tract*. In one the defect is beneath the septal leaflet of the tricuspid valve and, although still relatively high in the septum, it is not as closely related to the pulmonary artery ostium on the right ventricular side or to the aortic valve on the left ventricular aspect as the outflow type. The other type of inflow tract defect is lower in the muscular septum toward the apex and varies considerably in size.

An infrequent, but nevertheless clinically and surgically important, complication of the outflow tract type of ventricular septal defect is the involvement of an aortic cusp, usually the right, into the defect (Fig. 2). This may vary from a prolapse of the cusp into the defect due to lack of support of its margin to fibrous incorporation of the cusp into the defect. At times this cusp is unusually long and balloons freely into the defect.

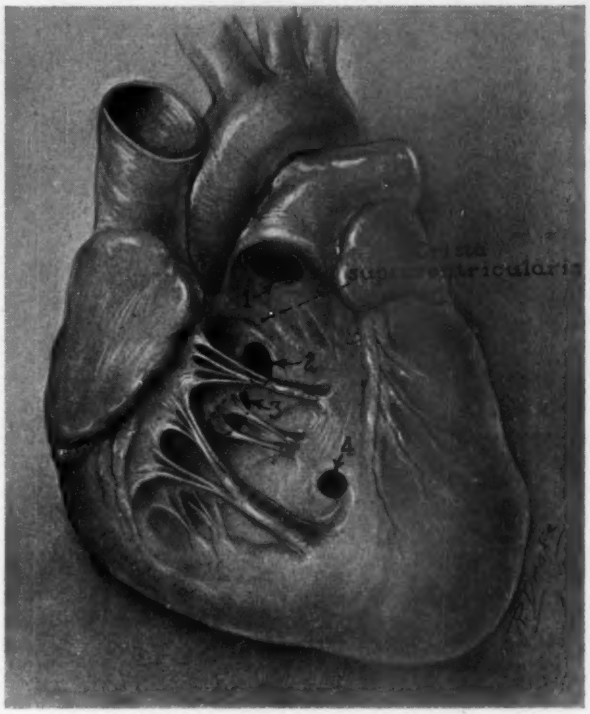


Fig. 1. Composite schematic drawing of right ventricular aspect of septum. (1) Outflow tract defect immediately beneath the pulmonary valve and superior to the crista supraventricularis. (2) Outflow tract defect inferior to the crista supraventricularis (most common site). (3) Inflow tract defect beneath septal leaflet of tricuspid valve. (4) Inflow tract defect near apex. From: Kirklin, J. W., Harshbarger, H. G., Donald, E. E. and Edwards, J. F. Surgical correction of ventricular septal defect; anatomic and technical considerations. *J. Thoracic Surg.*, 33: 45, 1957.

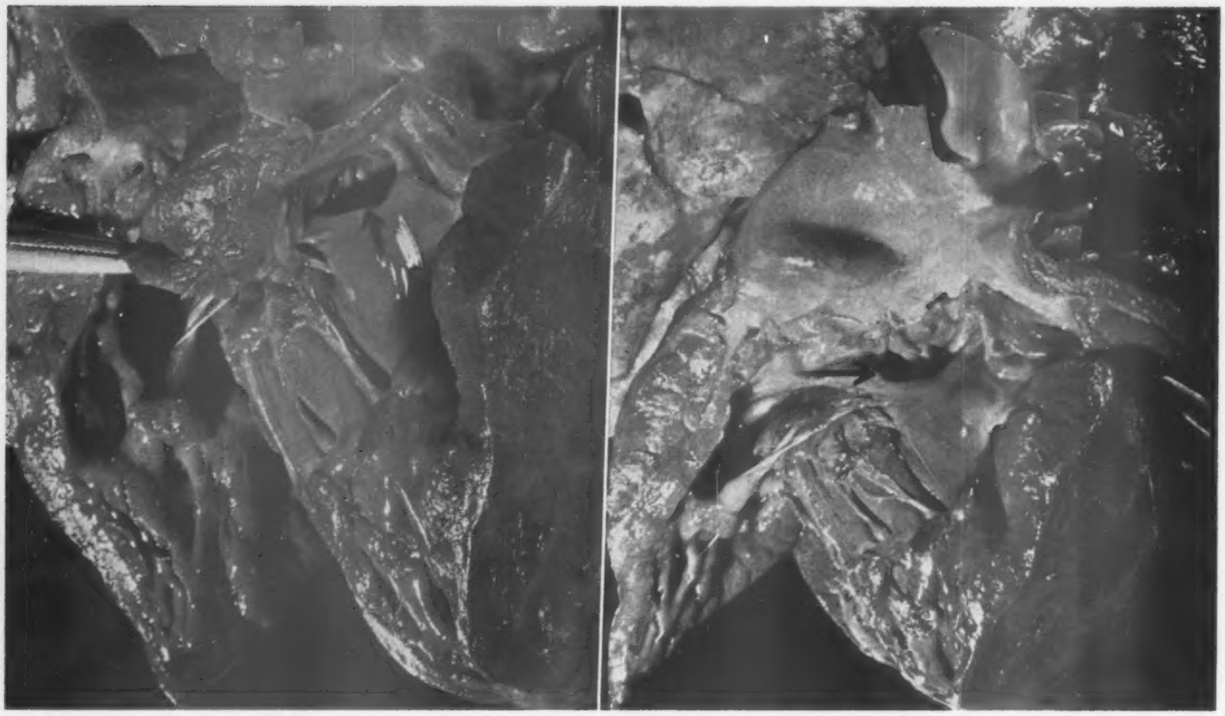
Hemodynamic Alterations

The hemodynamic alterations in ventricular septal defect are determined by several factors: (1) the size of the defect; (2) the resistance offered to left ventricular flow by the size of the aortic valvular orifice or by alteration in systemic pressures; and (3) the resistance offered to right ventricular flow by the size of the pulmonic valvular orifice, by alterations in pulmonary arterial pressure, and by obstructions in the outflow tract as represented by infundibular stenosis or by hypertrophy of the crista supraventricularis.

In the majority of patients with ventricular septal defects, and in this series in particular, no stenosis of either the aortic or pulmonary valves was evident. Infundibular stenosis likewise was ruled out by cardiac catheterization studies and by selective angiocardiography. Hypertrophy of the crista supraventricularis was indicated in some instances, and will be dealt with in a later section. Thus the size of the defect, and therefore the degree of flow, and the relative resistances in the systemic and pulmonary circuits are the determining factors leading to enhanced ventricular work and heart chamber size.

It is believed that the size of the defect and thus the amount of flow is not necessarily the cause of increased pulmonary vascular resistance, when one considers the infrequency of severe pulmonary hypertension in other situations with similar or larger left-to-right shunts. In atrial septal defects and in patent ductus arteriosus severe pulmonary hypertension is uncommon. Possibly, therefore, some inherent difference in the pulmonary vascular response exists in patients with ventricular septal defect as opposed to a less severe vascular "reactivity" in these other conditions.

Civin and Edwards[4] have suggested that the pulmonary arteries retain their fetal characteristics in such patients, although it is difficult



A B

FIG. 2. Two cm. diameter outflow tract ventricular septal defect (arrows). A, right ventricular aspect showing aortic cusps at upper margin of defect. B, left ventricular aspect showing the left posterior aortic cusp prolapsed into the ventricular septal defect.

to understand why this should be so in some instances and not so in others. The subsequent course then would be determined by their persistence, a regression toward normal with a drop in pulmonary resistance, or to secondary changes of further vascular obstruction then resulting in a greater increase in pulmonary resistance.

ROENTGENOGRAPHIC FINDINGS

Most of the cardiovascular roentgenographic findings are readily recognizable with the use of conventional radiographic technics. The criteria employed are those standard in the "Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels" of the New York Heart Association.[5]

The pulmonary vascular changes are better seen on films than on fluoroscopy. We believe, however, that despite the hazards of increased exposure to radiation during fluoroscopy, both to patient and physician, significant additional information is obtained to justify its use. The dynamic aspects of vascular pulsations in the lung vessels and aorta are visualized and thus make a diagnostic contribution. We have frequently noted left atrial enlargement on fluoroscopy but have failed to see it on conventional films. Closeness of the x-ray tube target to screen distance in fluoroscopy with its consequent distortions apparently enhances rather than hinders estimation of left atrial size. Deep inspiration, best obtained by the fluoroscopist from the patient, often has allowed interpretation of the lower left cardiac segment as right rather than left ventricular border, not differentiable on film. Proper positioning of the patient in the left anterior oblique position on fluoroscopy has afforded recognition of right atrial enlargement as well as differentiating left from right ventricle. Frequently this is not obtained with such certainty by conventional roentgenograms.

Roentgenographically patients with interventricular septal defect fall into four groups: (1) patients with normal heart size and normal pulmonary vasculature; (2) patients with normal heart size and abnormal pulmonary vasculature; (3) patients with slight enlargement of the left atrium and/or the left ventricle and varying degrees, usually minor, of increased pulmonary vascularity; and (4) patients with large hearts and increased pulmonary vascularity.

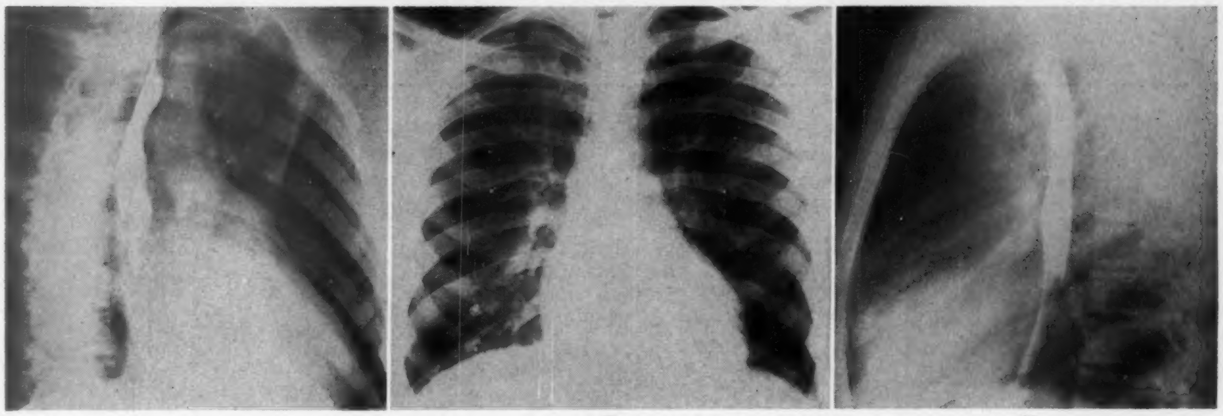


FIG. 3. Case 15. Roentgenograms in right anterior oblique (A), posteroanterior (B) and left anterior oblique (C) positions indicating some slight increase in pulmonary vascularity, no cardiac chamber enlargement and slight prominence of the pulmonary artery segment chiefly in the right anterior oblique position.

GROUP 1. NORMAL HEART SIZE AND PULMONARY VASCULATURE

This group (Table I) is comprised of twelve patients with no roentgenographic evidence of cardiac chamber enlargement or increased pulmonary pressure or flow. These patients showed a normal, or at most a slightly elevated, ratio of pulmonary artery pressure to femoral artery pressure, and rarely any significant degree of shunting of blood from left to right ventricle. In two such patients anatomical visualization of the defect was obtained. In both, the defect was small and located in the inflow portion of the right ventricle, underlying the septal leaflet of the tricuspid valve.

It would appear, therefore, that roentgenographically normal heart size and pulmonary vasculature can be correlated with normal or mildly elevated pulmonary artery pressures and mild degrees of left-to-right shunting of blood.

TABLE I

Group 1. Patients with Normal Heart Size and Pulmonary Vessels by X-Ray

Case No.	Age (yr.)	Pulmonary Artery Pressure (mm. Hg)	Pulmonary Artery Pressure / Femoral Artery Pressure Ratio (%)	Left-to-right Shunt (% over systemic flow)	Electro-cardio-gram	Pathology
1	4	45/10	35	313	N	...
2	15 mo.	30/9	33	82	LVH	5 mm. × 2 mm. inflow tract defect; lungs normal
3	5	37/15	30	111	LVH	5 mm. diameter inflow tract defect; lungs normal
4	4	20/10	22	130	N	...
5	9	25/7	23	42	N	...
6	11	25/10	18	30	N	...
7	5	26/12	26	66	LVH?	...
8	6	29/9	22	61	LVH	...
9	4	22/7	21	55	N	...
10	4	30/19	28	77	N (Inc. RBBB)	...
11	3	21/7	23	38	N (Inc. RBBB)	...
12	9	19/3	18	45	N	...

NOTE: The following abbreviations are used in all tables: N = normal. LVH = left ventricular hypertrophy. Inc. RBBB = incomplete right bundle branch block. RVH = right ventricular hypertrophy.

TABLE II

Group 2. Patients with Normal Heart Size and Abnormal Pulmonary Vasculature

Case No.	Age (yr.)	Right Ventricular Pressure (mm. Hg)	Pulmonary Artery Pressure (mm. Hg)	Pulmonary Artery Pressure / Femoral Artery Pressure Ratio (%)	Left-to-Right Shunt (% over systemic flow)	Electro-cardio-gram	Comment
13	9	88/6	44/14	30	188	RVH	Isolated "post-stenotic" dilatation of pulmonary artery only on x-ray; 12 mm. diameter outflow tract defect
14	4	60/11	43/12	43	77	LVH	Increased secondary and tertiary pulmonary vessels
15	16	51/0	32/3	24	32	N	Isolated "post-stenotic" dilatation of pulmonary artery only
16	8	34/0	28/11	25	46	N	Hilar dance

The limited anatomic studies suggest that these are small defects located in the inflow portion of the right ventricle.

GROUP 2. NORMAL HEART SIZE AND ABNORMAL PULMONARY VASCULATURE

In this group (Table II) there were four patients in whom heart size was normal, but significant abnormalities of the pulmonary vasculature were present. In two isolated dilatation of the main pulmonary artery segment with normal distal pulmonary vasculature was demonstrated, in one the size of the secondary and tertiary pulmonary vessels was increased and in one, fluoroscopy revealed hilar dance. The latter was the only patient who showed a hilar dance in the presence of normal pressures and mildly increased pulmonary flow.

The left-to-right shunt in this group was of no greater degree than in the patients in group 1. It should be noted, however, that in three of these patients systolic pressures were lower in the pulmonary artery than in the right ventricle. This suggests the existence of a "protection" of the pulmonary bed by hypertrophy of the crista supraventricularis in the outflow portion of the right ventricle. When this occurs the pulmonary artery pressures are but mildly or moderately elevated. Cardiac hypertrophy (as opposed to dilatation) is not recognizable roentgenographically, and occasional patients present a picture more consistent with isolated pulmonic valvular stenosis, i.e., a poststenotic dilatation of the pulmonary artery with normal hilar and peripheral vasculature (Fig. 3).

At surgery one of these patients (Case 13) showed a 12 mm. diameter outflow tract septal defect, but despite a location and size similar to those in the more advanced group roentgenographically and physiologically, the protective mechanism of the infundibular hypertrophy had apparently resulted in a striking difference in the degree of cardiac hypertrophy. The attractive theory of a "reactive" infundibular hypertrophy that protects the lungs against a high pulmonary blood flow has been suggested by Gasul.[6]

GROUP 3. MILD CARDIAC ENLARGEMENT AND VARIABLE PULMONARY VASCULARITY

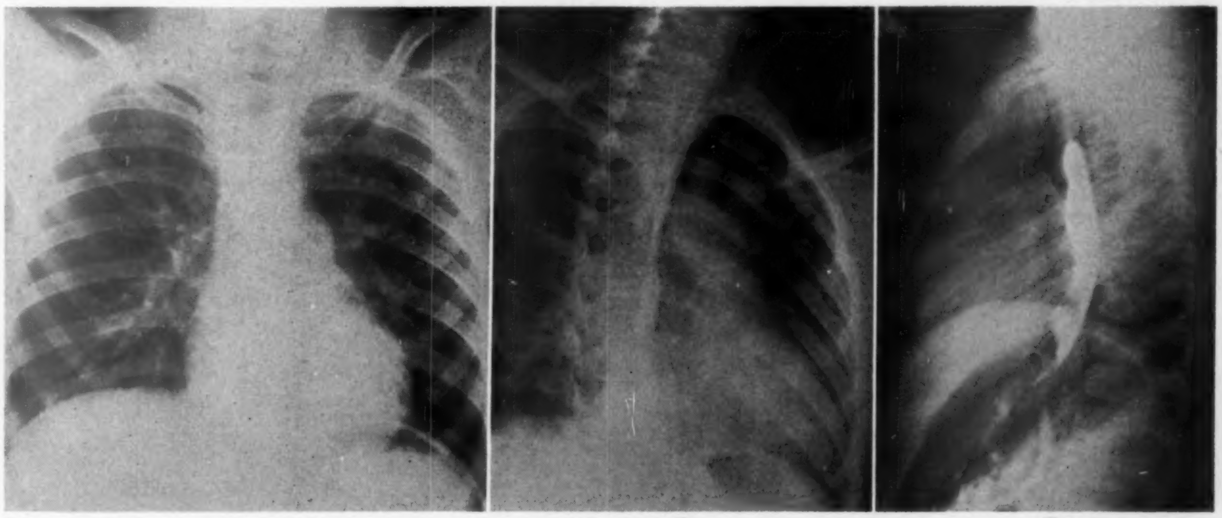
In this group (Table III) roentgenographic evidence of mild cardiac enlargement was present in nine patients. Of these, both slight left atrial and left ventricular enlargement was present in seven (Fig. 4), left ventricular enlargement in one, and left atrial enlargement only in one. This patient (Case 19) showed left ventricular hypertrophy by electrocardiogram. Only three of these patients had increased pulmonary vascularity.

TABLE III

Group 3. Patients with Slight Enlargement of Left Atrium and/or Left Ventricle by X-ray

Case No.	Age (Yr.)	Pulmonary Artery Pressure (mm. Hg)	Pulmonary Artery Pressure / Femoral Artery Pressure Ratio (%)	Left-to-Right Shunt (% over systemic flow)	Electro-cardio-gram	Comment
17	6	35/7	35	105	N	5 mm. diameter inflow tract defect; lung biopsy normal
18	2 1/2	45/18	40	171	LVH?	Increased pulmonary vasculature; 5 mm. diameter inflow tract defect; lung biopsy normal
19	6	40/19	38	33	LVH	5 mm. diameter inflow tract defect; lung biopsy normal
20	7	37/18	35	113	LVH?	
21	4	78/36	62	145	RVH?	Disproportionally increased pulmonary vasculature; 12 mm. diameter posterior outflow tract defect; lung biopsy normal
22	5	40/10	36	50	N (Inc. RBBB)	Slightly increased pulmonary vasculature
23	5	34/17	32	33	N	
24	10	37/8	29	18	LVH	Probable prolapsed aortic cusp with mild insufficiency; slight dilatation of aorta with expansile pulsations
25	2	20/10	23	161	LVH	

In the patients in group 3 the pulmonary artery pressures were mildly to moderately elevated, although the pulmonary flow was not significantly different from that obtained in those in group 1. Where anatomic correlation was obtained, the defect was small and located in the inflow portion of the right ventricle with one exception (Case 21). Here the defect was rather large, and located in the outflow tract. Significantly his pulmonary pres-



A B C

FIG. 4. Case 17. Roentgenograms in the posteroanterior (A), right anterior oblique (B) and left anterior oblique (C) positions indicating slight increase in pulmonary vascularity, questionable left ventricular enlargement and slight but definite left atrial enlargement (B and C).

TABLE

Group 4. Patients with Large Hearts

Case No.	Age (yr.)	Pulmonary Artery Pressure (mm. Hg)	Pulmonary Artery Pressure / Femoral Artery Pressure Ratio (%)	Left-to-Right Shunt (% over systemic flow)	Roentgenographic Findings	Hilar Dance
26	3	73/52	93	83	LV?; LA-N; RA 2+; RVO 3+; RVI 2+; PA 3+; pul. vasc. +	+
27	9	58/9	50	163	LVO 2+; LVI 2+; LA 2+; RA +; RVO 2+; RVI +; pul. vasc. +	+
28	4	69/34	69	257	LVO +; LVI +; PA 3+; pul. vasc. 3+	+
29	11	110/70	78	45	RV+; RA 2+; PA 2+; pul. vasc. N	0
30	3	67/52	85	118	RVO +; RVI +; PA 3+; pul. vasc. 2+	+
31	2	69/40	73	275	LV +; LA 3+; pul. vasc. 3+	0
32	2	43/14	41	218	LVO 2+; LA + ; PA 2+; pul. vasc. 2+	+
33	5 mo.	74/59	87	160	LV +; LA 2-3+; hypervascular lungs with slight hilar dilatation	+
34	5	108/46	85	138	LV +; LA +; RVO +; pul. vasc. +	+
35	8	94/62	104	100	LV +; LA 1-2+; RVO 2+; RVI +; PA 3+; pul. vasc. 2+	+
36	13	80/18	45	151	LV 3+; LA 2-3+; RV, RA ?; PA 3+; pul. vasc. 3+	+
37	6	38/15	42	180	LV 1-2+; LA +; PA 2+; pul. vasc. 2+	+
38	4	55/37	51	92	LV +; LA +; RV +; PA +; pul. vasc. +	0
39	3	40/21	39	91	RVO +; PA 3+; pul vasc. 2+	0
40	16 mo.	76/40	73	130	LV +; LA +; RVO, RVI 2+; PA 2+; pul. vasc. 3+	+
41	15	50/17	42	129	LVO; LVI 2+; LA +; RA +; RA +; PA N; pul. vasc. +	0
42	2	34/21	31	533	LV 3+; LA 2+; pul. vasc. 2+	0
43	6	111/74	112	167	LV 2-3+; LA 1-2+; RA ±; PA 3+; pul. vasc. 3+	+
44	2	75/0*	131	58	LV ?; RVO 3+; RVI 2+; PA 3+; pul. vasc. 3+	+
45	34	48/12	41	124	RV 2+; RA 2+; Rt. hilar branch +	0
46	26	90/57	84	286	LVO +; RVO +; PA 2+; pul. vasc. 2+	+
47	7	97/10	109	207	RV 3+; RA 3+; PA 2+; pul. vasc. 2+	+
48	9	35/24	32	82	LV 2-3+; LA 2+; RV 2+; aorta dilated	0
49	10	77/35	70	250	LVO 3+; LVI +; LA +; RVI +; PA 2+; pul. vasc. +	+
50	39	115/60	95	131	LV +; LA +; RV +; RA +; PA 3+; pul. vasc. 3+	+

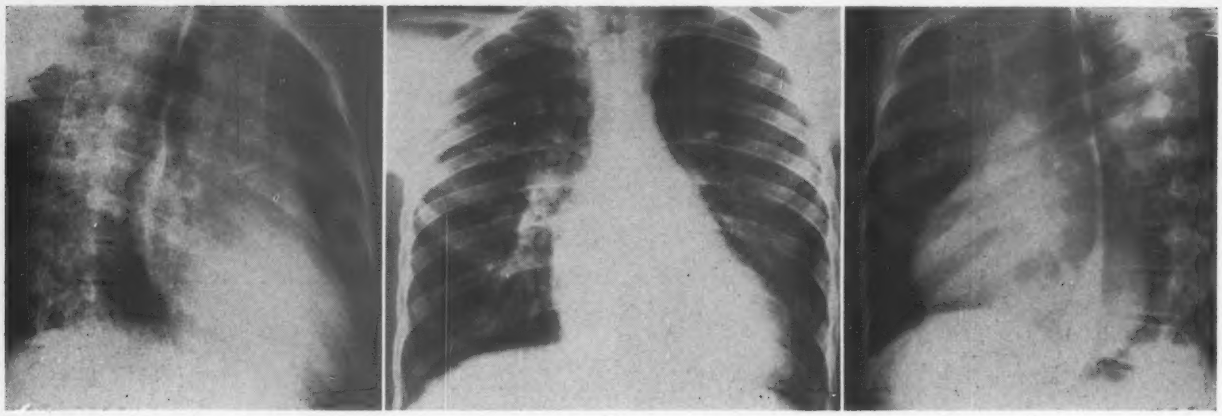
NOTE: N = normal. + = mild. 2+ = moderate. 3+ = severe. Comb. = combined ventricular hypertrophy. RVI = right ventricular inflow tract. Pul. Vasc. = pulmonary vasculature. LA = left atrium. RA = right

* Right ventricular pressure.

IV
and Increased Pulmonary Vasculature

Electro-cardio-gram	Ventricular Defect	Lung Biopsy	Comment
Comb.	14 × 6 mm. outflow tract	Normal	...
Comb.	14 × 10 mm. outflow tract	...	...
Comb.	25 mm. diameter outflow tract	Normal	...
RVH	3 inflow defects: largest near apex 15 × 20 mm. 2 smaller above	Severe hypertensive changes	Peripheral unsaturation (92%)
RVH	20 mm. diameter outflow tract	Increased perivascular fibrosis	Peripheral unsaturation (93%)
Comb.	25 mm. diameteı outflow tract	Mild hypertensive changes	...
LVH	20 mm. diameter inflow tract	Normal	...
Comb.	10 mm. diameter outflow tract	Normal	...
RVH; ?LVH	20 mm. diameter outflow tract	Mild perivascular fibrosis	Peripheral unsaturation (93%)
Comb.	35 mm. diameter outflow tract	Moderate hypertensive changes	Aortic insufficiency due to prolapsed cusp into defect
Comb.	12 × 5 mm. outflow tract	...	...
Comb.	...	...	...
LVH	...	...	...
RVH	...	...	...
Comb.	20 mm. diameter outflow tract	...	...
Comb.	...	...	RV pressure 87/0. Crista supraventricularis constriction
LVH	10 mm. diameter outflow tract	...	...
RVH	2 defects: (1) outflow tract 13 × 7 mm. (2) low toward apex 25 × 15 mm.	...	Basically single ventricle. Peripheral unsaturation (94%)
Comb.	...	...	Pulmonary artery not entered. Peripheral unsaturation (91%)
RVH	25 mm. diameter outflow tract	...	Infundibular hypertrophy marked RV pressure 66/0
Comb.	...	...	Peripheral unsaturation (92%)
Comb.	Single ventricle	...	Peripheral unsaturation (85%)
LVH	...	...	Aortic insufficiency probably due to prolapsed cusp into defect
Comb.	2 defects: (1) 25 mm. diameter outflow tract. (2) 35 mm. diameter lower in outflow tract	...	Peripheral unsaturation (93%)
LVH; RBBB	...	...	Peripheral unsaturation (88%)

LVO = left ventricular outflow tract. LVI = left ventricular inflow tract. RVO = right ventricular outflow tract. atrium.



A B C

FIG. 5. Case 41. Roentgenograms in right anterior oblique (A), posteroanterior (B) and left anterior oblique (C) positions indicating slight increase in pulmonary vascularity, moderate left ventricular enlargement (B and C), slight left atrial enlargement (A) and slight right atrial enlargement (C).

sures were the highest recorded in the patients in group 3 (although flow was not) and roentgenographically there was considerable disproportion between the great degree of pulmonary vascularity and the slight cardiac enlargement.

GROUP 4. LARGE HEARTS AND INCREASED PULMONARY VASCULARITY

Half the patients in this series (Table IV) fell into the severe category with large hearts and increased pulmonary vasculature. In this group multiple chamber enlargement by x-ray was the rule, and unmistakable pulmonary hypervascularity was evident. Almost invariably severe pulmonary hypertension was present and the degree of left-to-right shunt was considerably greater than in the other groups of patients (Figs. 5, 6, 7, 8 and 9).

Exceptions were rare and as a rule an acceptable explanation was apparent. Thus one patient (Case 45) showed a right ventricular pressure considerably higher than the pulmonary artery pressure and at operation a marked degree of protective infundibular hypertrophy. Another patient (Case 32) had a considerably greater degree of left-to-right flow (through a large 2 cm. diameter defect) than pulmonary artery pressure elevation. One patient (Case 44) undoubtedly has an aortic cusp prolapsed into the ventricular defect; her degree of cardiac enlargement is related more to the severe aortic insufficiency than to the functional disturbances produced by the septal defect itself.

In the patients in group 4 the defect is always large and as a rule it is located in the outflow portion of the right ventricle. Patients with a single ventricle or those who have mul-

A B C

FIG. 6. Case 28. Roentgenograms in right anterior oblique (A), posteroanterior (B) and left anterior oblique (C) positions indicating moderate to marked pulmonary hypervascularity, prominence of the main pulmonary artery segment and increased width of the right pulmonary artery branch (B); left ventricular enlargement (B and C), left atrial enlargement (A), and right atrial enlargement (C).

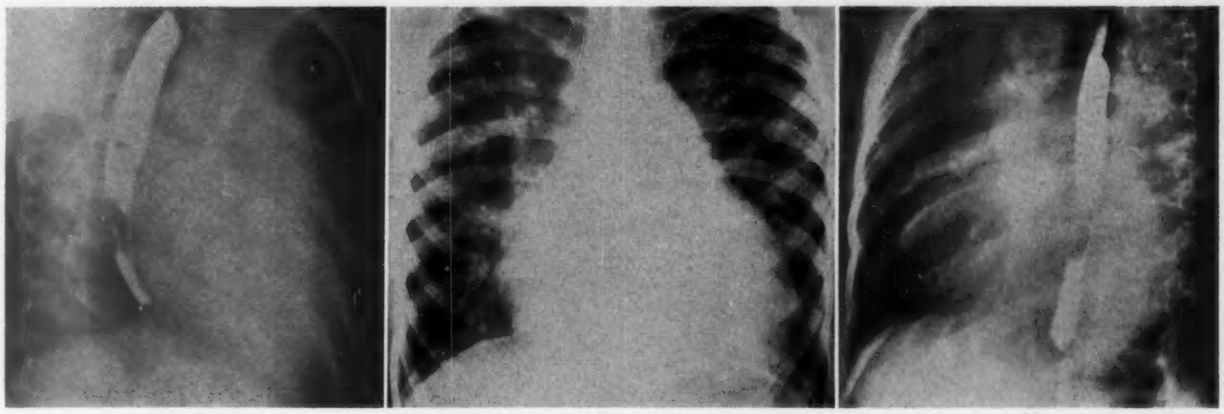


FIG. 7. Case 27. Roentgenograms in the right anterior oblique (A), posteroanterior (B) and left anterior oblique (C) positions indicating increased pulmonary vascularity, moderate left ventricular enlargement (B and C), slight to moderate left atrial enlargement (A), and moderate right atrial enlargement (C).

tiple large defects in the lower part of the ventricular septum, and thus basically a single ventricle, are similar in their physiologic and roentgenographic aspects.

Patients who have ventricular septal defects with severe pulmonary hypertension and varying degrees of "functional" over-riding of the defect by the aorta and thus peripheral arterial unsaturation, fulfill the criteria of the *Eisenmenger syndrome*.[7,8] Such patients show predominantly or exclusively right-sided enlargement of the heart and a large main pulmonary artery. Except in infants and young children (the "pulmonary vascular obstruction syndrome" of Nadas et al.[9]) the left atrium is smaller than in the group with pure left-to-right shunts. All but one patient (Case 29) with the Eisenmenger syndrome showed a hilar dance, and in this patient the hilar and secondary pulmonary vessels were normal (Fig. 10).

We have not been able to notice the diminution of peripheral pulmonary vasculature and clear lung fields described by others.[10,11] In fact, we have been struck by the somewhat higher incidence of such findings in patients with mitral stenosis and severe pulmonary hypertension than we have seen in the Eisenmenger type of ventricular septal defect.[12]

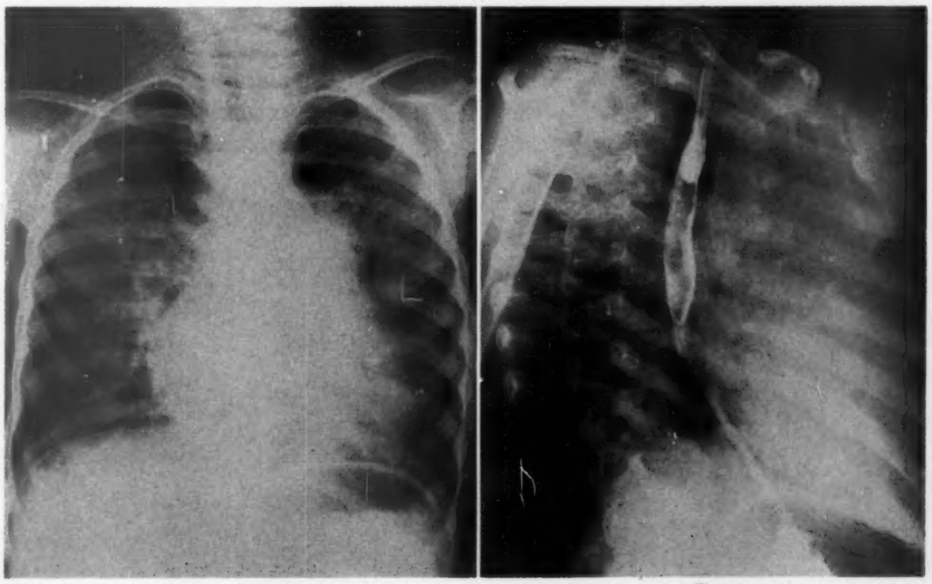


FIG. 8. Case 26. Roentgenograms in the posteroanterior (A) and right anterior oblique (B) positions indicating moderate increase in pulmonary vascularity, prominent pulmonary artery trunk, and increased width of right pulmonary artery (pulmonary hypertension) in (A), slight left atrial enlargement (B), and only slight left ventricular enlargement (B).

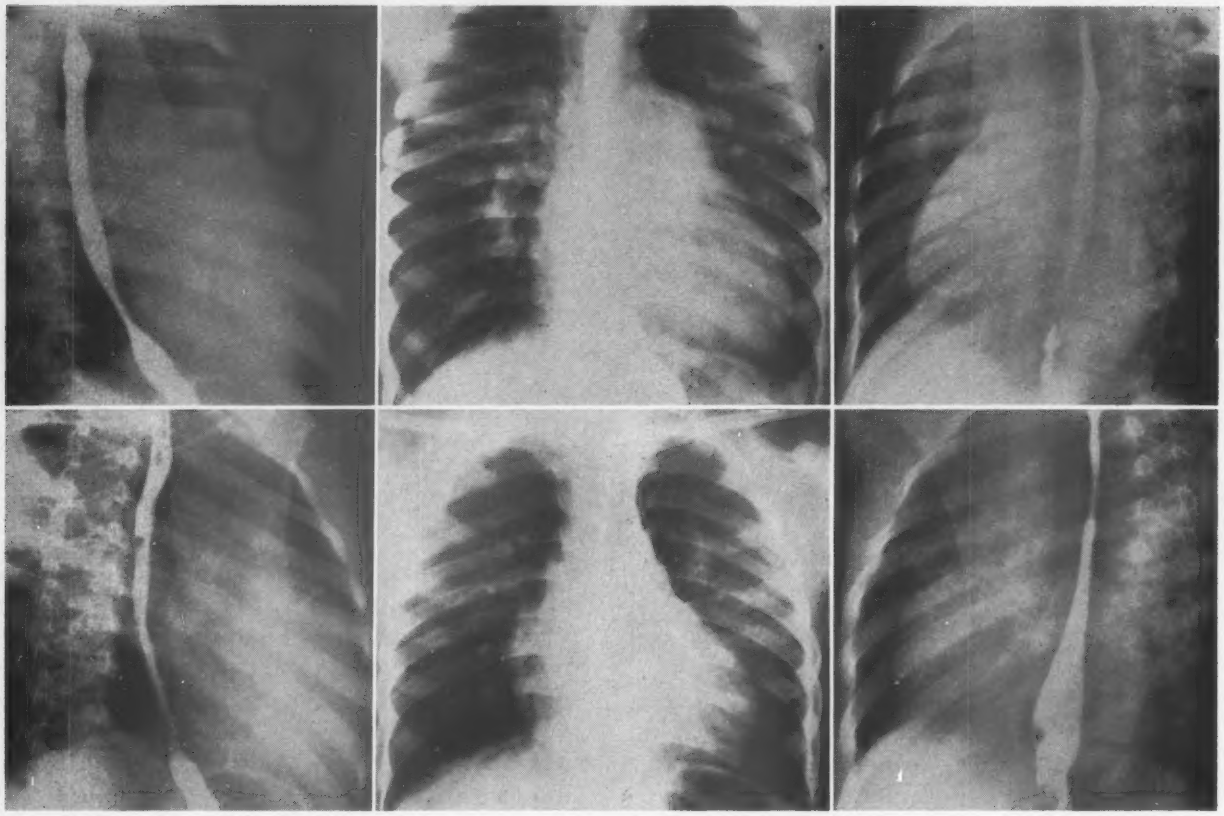


FIG. 9. Case 34. Roentgenograms before operation (top row) indicate pulmonary hypervascularity, prominent pulmonary artery trunk and hilar vessels, moderate left ventricular enlargement and questionable left atrial enlargement. Roentgenograms fourteen months postoperatively (bottom row) show diminished prominence of the pulmonary artery trunk, heart chambers unchanged; hypervascularity formerly present has disappeared along with the prominent hilar vessels.

A *hilar dance* was found on fluoroscopy only in the group with severe pulmonary hypertension with one exception (Case 16). A dance occurs only when a large outflow tract septal defect, a single ventricle, or its equivalent, is present. There is no apparent correlation with the pulse pressure in the pulmonary artery or the size of the shunt *per se* as determined by catheterization figures. It would appear that a hilar dance in ventricular septal defect can only be explained by a direct thrust of left ventricular blood into the pulmonary artery.

FIG. 10. Case 29. Eisenmenger's syndrome. This patient also shows an unusual 90 degree dextrorotation of the heart with partial displacement into the right side of the chest. The pulmonary artery trunk is prominent. The right ventricle and right atrium are slightly enlarged. The left ventricle and atrium are apparently normal in size.

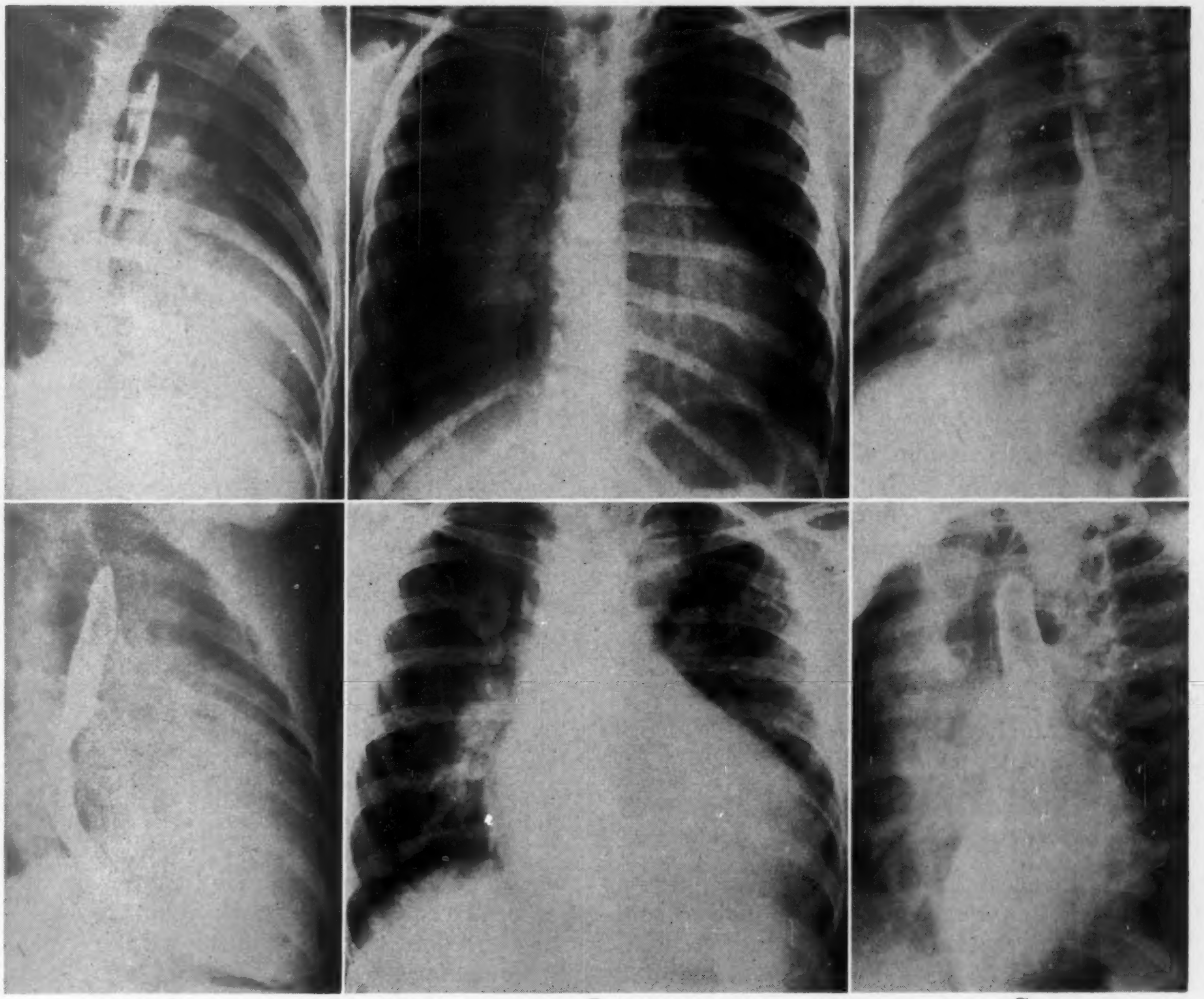


FIG. 11. Case 48. Roentgenograms depicting ventricular septal defect with prolapsed aortic cusp. The films in lower row were taken seven years after those in upper row. Note the marked increase in the size of the left ventricle (B and C) and left atrium (A), the marked dilatation of the aorta (B and C) and the increase in pulmonary vascularity (B).

Aortic insufficiency due to prolapse or incorporation of an aortic cusp into the septal defect will result as a rule in a disproportionately increased size of the left ventricle and the left atrium with expansile pulsations of a dilated aorta seen on fluoroscopy (Fig. 11). These changes are obviously a function of the severity of the aortic valvular insufficiency.

In several other lesions of this type, corroborated at operation or by postmortem examination, the defect was unusually large. Pulmonary pressure and flow had been very high. The unusual hemodynamic data in two patients (Cases 24 and 48) perhaps may be explained. If the incorporation of the valve leaflet into the defect has resulted in an aortic orifice larger than that of the defect, the greater amount of left ventricular blood will be delivered to the periphery rather than shunted into the pulmonary circuit. The degree of pulmonary flow and hypertension anticipated for the actual size of the defect is thus diminished.

ASSOCIATED CARDIAC DEFECTS

Associated congenital cardiac defects, such as coarctation of the aorta or patent ductus arteriosus, do not seem to have intensified either the left-to-right shunt or the degree of pulmonary hypertension beyond that attributable to the septal defect alone. Correspondingly in none of these patients (not included in this tabulated series) has the roentgenographic picture differed, other than due to the additional findings in coarctation such as decreased size of

the aortic knob, presence of a dilated left subclavian artery, or rib-notching. An associated patent ductus arteriosus has not resulted in additional aortic dilatation. In no patients with combined ventricular septal defect and patent ductus arteriosus have we been able to detect the "infundibular sign"[13] recognizable roentgenographically in about 50 per cent of patients with an isolated patent ductus arteriosus.

ANGIOCARDIOGRAPHIC FINDINGS

Only six patients had positive angiocardiograms (Cases 19, 21, 22 in group 3, and 29, 36 and 48 in group 4). The positive findings were those of reopacification of the right ventricle, pulmonary artery or both. The opacifying substance was injected into the right ventricle in all (selective angiocardiography); on a previous occasion one patient had demonstrated similar findings by conventional venous angiocardiography.

Neither the size nor the location of the defect apparently had any relationship to the reopacification. The role of general or selective angiocardiography, therefore, was not striking or regarded as an important diagnostic tool.

Differential Diagnosis

The utilization of roentgenographic criteria alone, without knowledge of the clinical and electrocardiographic findings for differentiating the various congenital and certain acquired cardiac lesions, has extremely limited value. Most conditions that may simulate ventricular septal defect roentgenographically can be eliminated from consideration on clinical grounds.

In the types of cardiac involvement that result in left ventricular and/or left atrial enlargement with varying degrees of pulmonary artery and vascular or aortic prominence, there are rather characteristic murmurs (and thrills). This group includes patent ductus arteriosus, congenital aortic or subaortic stenosis, and rheumatic mitral insufficiency or acquired aortic valvular disease.

Patients who show normal heart size and abnormal pulmonary vasculature, particularly if there is a significant "poststenotic" type of dilatation of the pulmonary artery, may be similar roentgenographically to patients with mild pulmonary valvular, or combined valvular and infundibular stenosis, with a normal aortic root. Clinical differentiation here is not difficult. Mild infundibular stenosis alone, however, with its murmur and thrill lower down along the left sternal border, at times may offer difficulty on clinical and electrocardiographic as well as roentgenographic grounds. Here, cardiac catheterization and angiocardiography are of value.

In the majority of patients with the larger ventricular septal defects and moderate to severe pulmonary hypertension, diagnosis can be made on the basis of clinical findings. The greatest potential for diagnostic difficulty occurs with infants and very young children. In such patients, a *patent ductus arteriosus* with sufficient pulmonary diastolic hypertension may be clinically and electrocardiographically indistinguishable from ventricular septal defect. Unfortunately, roentgenography is also similar so that cardiac catheterization and at times only aortography have been helpful or deciding factors. The presence of a large pulsating aorta in patients with patent ductus arteriosus at times is helpful[14] but it does not occur frequently enough to be of great differential value.

In the occasional infant and young child the clinical findings of *atrial septal defect* may simulate those of ventricular defect. Here, on electrocardiogram the incomplete right bundle branch block pattern may be present in both. At such times roentgenography has proved of decided value. Only in the ventricular defect is left atrial enlargement present despite the similarity in right-sided enlargement, hypervascularity of the lungs and even a hilar dance in both conditions.

Endocardial cushion defects in infants and young children may be indistinguishable clinically and even roentgenographically, depending on the degree of mitral valvular involvement. Thus, if a significantly cleft mitral valve exists with the ostium primum defect, the combination of mitral insufficiency plus the left-to-right shunt results in biventricular and biatrial hypertrophy with pulmonary plethora—the same as occurs in severe advanced ventricular defect. To date, based on autopsy corroboration, accurate differentiation depends on the electrocardiogram showing left axis deviation with incomplete right bundle branch block or right ventricular hypertrophy with evidence of a shunt at the atrial level on cardiac catheterization.[15]

Patients with *ventricular septal defect with aortic insufficiency* by x-ray and fluoroscopy may simulate those with a large flow through a patent ductus arteriosus, resulting in biventricular and left atrial hypertrophy, a large expansile aorta and hilar dance. It has been said that

clinically they may simulate each other, too, but careful auscultation will avoid this error, for murmurs of a patent ductus are more localized to the second and third left interspaces, are of different intensity and pitch and are continuous or "machinery" in type, whereas the diastolic murmur of associated aortic insufficiency is higher pitched and blowing in character and transmitted down lower along the left sternal border.[16]

In differentiating patients with the Eisenmenger syndrome, difficulty is encountered in the patient with patent ductus arteriosus or atrial septal defect with severe pulmonary hypertension and reversal of flow with peripheral arterial unsaturation, and in the patient with primary pulmonary hypertension. Clinically murmurs may be absent or indistinguishable by virtue of location; the electrocardiogram is often that of pure right ventricular enlargement. Roentgenographically pure right-sided enlargement of the heart with equal degrees of pulmonary vascular enlargement plus hilar dance may be present in all.

Most will be differentiated by further study with selective angiocardiography or cardiac catheterization but even here, differential oxygen saturations will not be necessarily sufficiently diagnostic in the presence of right-to-left shunts. Traversal of the defect or ductus by the catheter may be the only acceptable diagnostic feature. An angiocardiogram may show early filling of the supracardiac aorta in the patient with the Eisenmenger syndrome whereas with patent ductus arteriosus it may show early filling of the descending aorta from the pulmonary artery.

Summary and Conclusions

The cardiovascular roentgenographic changes in ventricular septal defect show a broad spectrum from entirely normal to evidence of enlargement of all chambers and marked pulmonary plethora. A good correlation between size and location of the defect, resulting left-to-right shunt, and concomitant degree of pulmonary hypertension has been demonstrated. These changes have been described.

In fifty consecutive patients with ventricular septal defect in whom full physiologic data were obtained, the following correlations were noted:

1. One-quarter showed normal roentgenograms with normal or mildly elevated pulmonary artery pressures and presumably small inflow tract defects.

2. A small group showed normal cardiac chambers but minor abnormalities of the pulmonary vasculature. Here the defect is large but crista supraventricularis hypertrophy maintains the pulmonary artery pressure at mildly elevated levels.

3. One-fifth showed only slight enlargement of the left atrium and/or left ventricle with at most mild hypervascularity of the lung fields. These patients as a rule have no more than moderately elevated pulmonary artery pressures and flows, and small inflow tract defects.

4. One-half had moderate to severe pulmonary hypertension. In this group there are greater degrees of left-sided enlargement and varying degrees of right-sided enlargement, the latter increasing proportionately with the degree of pulmonary vascular resistance and approaching reversal of shunt. Here the defect is large and in the outflow tract, or basically a single ventricular chamber exists. A hilar dance occurs only in the presence of severe pulmonary hypertension and is a function of direct jetting of left ventricular blood into the pulmonary artery.

Associated incorporation of an aortic valve cusp into the ventricular defect results in disproportionate left ventricular and atrial enlargement and aortic dilatation. Only in this group will there be significant exceptions to the general conclusion that pulmonary artery pressures less than 45 mm. Hg and 20 mm. Hg diastolic commonly will be associated with normal cardiovascular roentgenograms or at most, mild degrees of left atrial and/or left ventricular enlargement and minimal pulmonary hypervascularity.

Acknowledgment

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References

1. Becu, L. M., Fontana, R. S., Du Shane, J. W., Kirklin, J. W., Burchell, H. B. and Edwards, J. E. Anatomic and pathologic studies in ventricular septal defect. *Circulation*, 14: 349, 1956.
2. Kirklin, J. W., Harshbarger, H. G., Donald, D. E. and Edwards, J. E. Surgical correction of ventricular septal defect: anatomic and technical considerations. *J. Thoracic Surg.*, 33: 45, 1957.
3. Cournand, A., Baldwin, J. S. and Himmelstein, A. Cardiac Catheterization in Congenital Heart Dis-

ease, pp. 26–29. New York, 1949. The Commonwealth Fund.
4. Civin, W. H. and Edwards, J. E. Pathology of the pulmonary vascular tree. Comparison of intrapulmonary arteries in Eisenmenger complex and in stenosis of ostium infundibuli associated with biventricular origin of the aorta. *Circulation*, 2: 545, 1950.
5. Nomenclature and Criteria for the Diagnosis of Diseases of the Heart and Blood Vessels, 5th ed., pp. 86–131. New York, 1953, New York Heart Association, Inc.
6. Gasul, B. M., Dillon, R. F., Vrla, V. and Hart, G. Ventricular septal defects. Their natural transformation into those with infundibular stenosis or into the cyanotic or non-cyanotic type of tetralogy of Fallot. *J. A. M. A.*, 164: 847, 1957.
7. Selzer, A. Defect of the ventricular septum: Summary of 12 cases and review of the literature. *Arch. Int. Med.*, 84: 798, 1949.
8. Selzer, A. and Laquer, G. L. The Eisenmenger complex and its relationship to the uncomplicated defect of the ventricular septum. Review of 35 autopsied cases of the Eisenmenger complex, including 2 new cases. *Arch. Int. Med.*, 87: 218, 1951.
9. Fyler, D. C., Rudolph, A. M., Wittenborg, M. H. and Nadas, A. S. Ventricular septal defect in infants and children: a correlation of clinical, physiologic and autopsy data. *Circulation*, 18: 833, 1958.
10. Kjellberg, S. R., Mannheimer, E., Rudhe, U. and Jonsson, B. Diagnosis of Congenital Heart Disease, p. 269. Chicago, 1955. Year Book Publishers Inc.
11. Keats, T. E., Kreis, V. A., and Simpson, E. Roentgen manifestations of pulmonary hypertension in congenital heart disease. *Radiology*, 66: 693, 1956.
12. Schwedel, J. B., Escher, D., Aaron, R. S. and Young, D. The roentgenologic diagnosis of pulmonary hypertension in mitral stenosis. *Am. Heart J.*, 53: 163, 1957.
13. Jönsson, G. and Saltzman, G. F. Infundibulum of patent ductus arteriosus—a diagnostic sign in conventional roentgenograms. *Acta Radiol.*, 38: 8, 1952.
14. Gonzalez-Cerna, J. L. and Lillehei, C. W. Patent ductus arteriosus with pulmonary hypertension simulating ventricular septal defect. Diagnostic criteria in ten surgically proven cases. *Circulation*, 18: 871, 1958.
15. Mark, H. M. and Young, D. The diagnosis of ostium primum defects. *Clin. Res.*, 7: 17, 1959.
16. Mark, H. M. and Young, D. Acyanotic cardiac lesions with continuous murmurs simulating patent ductus arteriosus. In: Proceedings of the Twenty-eighth Scientific Sessions of the American Heart Association. *Circulation*, 12: 747, 1955.

Considerations Involved in the Selection for Surgery of Patients with Ventricular Septal Defects*

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THE closure of a ventricular septal defect is intended to improve or correct the abnormal hemodynamic state and thereby insure the patient of a longer and more productive life. This can now be accomplished in properly selected patients and under ideal circumstances with a relatively low and acceptable risk. The mortality and morbidity of the procedure is certain to decrease further in the immediate future.

In view of the relatively benign nature of small defects, surgery is not deemed advisable in this group of patients at the present time. There exists another group of patients with large ventricular septal defects and severe elevation of pulmonary vascular resistance with right-to-left shunting of blood in whom the risk of operation is considered prohibitive.[1]

In an attempt to delineate more clearly the natural history of this defect, our experience has been reviewed. During the past eight years there have been 300 patients who, after careful clinical evaluation, have been considered to have a defect in the ventricular septum as the sole anomaly. Complete cardiac catheterization studies performed in the routine manner were obtained in 133 of these patients. The evaluation of these patients, together with the published experiences of others, form the basis for the opinions discussed here. The findings in these patients have been evaluated in an attempt to determine the characteristics of the ideal candidate for closure of the defect. The course followed by all patients with this defect has been examined closely, for knowledge derived from such a study will aid in determining when surgical intervention should be advised.

NATURAL HISTORY OF THE DISEASE

Average Life Span: The course of patients with ventricular septal defects has been reviewed in an attempt to determine life span and in an effort to decide if there is need for considering surgical intervention to be of an urgent nature.

It is difficult to be certain of the mean survival age, although the average age of death in Abbott's fifty patients was fifteen years with the oldest patient in her series living to forty-nine years of age.[2] This form of study, an autopsy series, certainly does not reflect an accurate evaluation of the life expectancy. There are many reports of patients living to the age of sixty years or more. It is most probable, however, that the defects in these latter patients were small. In our series of 300 patients, there are only eight patients living over the age of forty years. This represents less than 3 per cent of the total. It is therefore clear that the life span of the patient with a ventricular septal defect will be very considerably shortened and that successful surgical correction would prolong the lives of many.

The Critical First Two Years: The periods of life when death is most apt to occur and the causes of death must now be examined. It would appear that the first eighteen months of life are the most critical period for patients with a ventricular septal defect.[3,4] Of the 300 patients in our series, eleven have died, to our knowledge, during the period of observation. This figure excludes ten patients who died following corrective surgery. Eight of these patients died during the first six months of life

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and a ninth died at the age of fifteen months. One patient, with a very high pulmonary vascular resistance who was classified in the Eisenmenger group, died suddenly at the age of three and a half years. Postmortem examination revealed no immediate cause for the sudden death. Microscopic examination of the lungs showed a considerable degree of intimal fibrosis and medial muscular thickening of the small pulmonary arteries. The eleventh patient, a forty-four year old man, died from acute bacterial endocarditis. Necropsy revealed a defect 4 mm. in diameter in the fibrous portion of the ventricular septum.

Congenital heart disease was not suspected in five of the nine infants. They entered the hospital with a diagnosis of pneumonia and died within hours. A systolic murmur was present and a diagnosis of a congenital heart lesion was entertained in the remaining four infants. These died despite full medical treatment for their congestive failure and pneumonia. The size of the defects in the ventricular septum ranged from 3 to 12 mm. in diameter.

During the same period, twelve patients entered the hospital with congestive heart failure and survived with medical management. Five of these patients were aged six months or less. Two were between four and six years of age and the remaining patients were adults. Four additional patients in our series were hospitalized elsewhere and treated for congestive heart failure during the first eighteen months of life. Thus, a total of twenty-five patients were hospitalized with congestive heart failure and pneumonia during this period of eight years. Eighteen of these patients were below the age of eighteen months at the time of treatment. Nine survived with medical management and nine died, while a diagnosis of congenital heart disease was not considered in five of the latter group.

It is apparent, then, that the first two years of life are a very critical period and that the majority of patients who die with ventricular septal defects do so during this period of life. This has also been the experience of others.[5]

Surgery During First Two Years of Life: Can corrective surgery be expected to salvage many of these patients who die during this critical period? A signifiaant number of these patients enter the hospital and die quickly before the diagnosis is entertained. The mortality of open heart surgery in patients with congestive failure during the first eighteen months of life is high, probably in the order of 50 per cent. Our own experience is in keeping with that of others relative to medical treatment; namely, that about 50 per cent of infants in congestive heart failure will survive with this form of management. Therefore, in view of the results of medical treatment and the high surgical mortality of patients in this group, it is difficult to evaluate the advisability of surgery. Certainly, the rate of salvage will be low at the present time. Nevertheless, it is anticipated that the risk of surgery will continue to decrease in this age group as experience increases. This must follow if we are to save many of the patients who die with this anomaly.

However, there is at this time a definite place and indication for the palliative procedure of *banding the pulmonary artery* in some of these patients.[6] The mortality is significantly lower and this operation may well permit the patient to survive this critical period. Corrective surgery may then be accomplished at a later date.

Life History Between Ages Two and Ten Years: Following this critical phase, there appears to be a golden period in the natural history of this defect. Patients surviving the first two years tend to do well during the next decade of their life. An occasional patient will appear with congestive failure between the ages of two and five years, but this is unusual. In our experience, there is little deterioration in the general condition during this period.

The electrocardiogram remains relatively stationary and there is little or no evidence of increasing right ventricular hypertrophy, a finding that would reflect increasing pulmonary arterial resistance and pressure.[7] Serial films of the chest also indicate that progressive increase in heart size is rare. In fact the opposite usually occurs; namely, the heart tends to become somewhat smaller in relation to the size of the thorax as the child grows. Repeated physiologic studies obtained by cardiac catheterization as observed by Fyler and Weinberg and associates,[7,8] together with our own studies, reveal that the hemodynamic state is also relatively stationary during this period. Evidence of progressive increase in pulmonary vascular resistance and pulmonary artery pressure is unusual. Therefore, there is seldom an urgent need for surgical intervention between the ages of two and ten years if the pulmonary arteriolar resistance is normal or only slightly elevated. While some progression of the pulmonary vascular changes occurs in patients with a

normal pulmonary vascular resistance the changes are slight during this period.

Life History Following Adolescence: At about the time of adolescence, a tendency for the development of increasing pulmonary vascular resistance begins. This is the beginning of a downhill course for many patients with this defect. It is the result of the development of obliterative pulmonary vascular disease and is due to the appearance of intimal fibrosis with the existing thickened media, and possibly miliary embolization or arterial thrombosis. It is difficult at this time to determine why it develops earlier in the natural history of the disease in some patients than in others. We have followed up five patients who developed congestive failure with increasing pulmonary vascular resistance after the age of eighteen years. The major limiting factors in the natural history of this anomaly probably are the development of obliterative pulmonary vascular disease and myocardial insufficiency.

The occurrence of acute or subacute bacterial endocarditis is a danger existing at all ages, but is relatively uncommon during the first few years of life. In recent years, since the advent of antimicrobial therapy, it constitutes less of a threat to life.

FACTORS DETERMINING CLINICAL COURSE AND LIFE HISTORY

Let us now speculate as to the facts that would seem to determine the course of patients with a ventricular septal defect. The die is cast at birth, deciding the general course that patients will follow. This course is largely governed by the relationship between the size of the defect in the ventricular septum and the cross-sectional area of the aortic orifice, although the position of the defect may also be of some importance. The relationship may alter somewhat on occasions as the patient grows, and although this is not common, children should be followed up carefully at frequent intervals during the early years of life.

Small Septal Defects: Patients with small ventricular septal defects have little increase in pulmonary artery blood flow and pressure. The resistance to blood flow from the left to the right ventricle and thence into the pulmonary artery, lies at the site of the small defect in the ventricular septum and limits the volume of the shunt and maintains the normal difference in pressure between the two ventricles. These patients, by and large, do extremely well and may be observed in early adulthood or later in life with but slightly enlarged hearts and relatively normal pulmonary vascular resistance. The pulmonary vascular bed is protected from increased flow and increased pressure from birth and there is a normal regression of the fetal pattern of the small pulmonary arteries. This protection further prevents the development of changes in the pulmonary vascular bed, giving rise to increased resistance, until relatively late in the lives of some of these patients. Occasionally one sees a patient during the first months or years of life who dies and at necropsy a ventricular defect is found of a size that would appear not to have been pertinent to the death of the patient, yet no other cause for death is readily apparent.

Very Large Septal Defects: At the other end of the spectrum is the patient with the very large ventricular septal defect with marked increase in pulmonary vascular resistance and no significant difference between the systolic pressures of the two ventricles. The cross-sectional area of the defect in the ventricular septum approaches or may exceed that of the aortic orifice. Thus, the defect itself does not in any significant way limit the volume of the pulmonary artery blood flow or the transmission of left ventricular pressure through the right ventricle and into the pulmonary vascular bed. Under these circumstances, there are two outlets of relatively equal size competing for the output of the left ventricle. The relationship of the resistances of the systemic and pulmonary vascular beds governs the volume of blood flow into each system.

Under these conditions, the normal regression of the fetal pattern of the pulmonary vessels does not occur and the increased resistance within the pulmonary vascular bed limits the flow into this system. Should there be normal regression and development of normal pulmonary vascular resistance, then the output of the left ventricle would be predominantly into the pulmonary vascular bed, flooding this system and resulting in an inadequate systemic output, and the patient would not survive. The fact that some of these patients do survive indicates that high pulmonary vascular resistance is present from birth and these patients fall into the so-called Eisenmenger group.

Moderate-Sized Septal Defects: The majority of patients with ventricular septal defects fall somewhere in between the two groups that have been outlined. The size of the ventricular defect in

these patients is such that it offers a varying degree of obstruction to shunt flow into the pulmonary vascular bed. There is regression in whole or in part of the fetal pattern with reduction in pulmonary vascular resistance. Patients with defects of a certain size will then have high pulmonary artery blood flow and in these patients the development of congestive heart failure may occur. These form a considerable percentage of the total patients with ventricular septal defects and many of this group constitute the ideal candidates for surgical intervention.

Let us now examine the clinical profile of this type of patient.

Clinical Evaluation of the Ideal Candidate for Surgery

Of our 133 patients with adequate cardiac catheterization studies, the pulmonary artery blood flow was at least three times the systemic flow in twenty-one patients. The total pulmonary vascular resistance per square meter of body surface area was less than 8 units. An additional twenty-three patients had pulmonary blood flows between two and three times the systemic blood flow and pulmonary vascular resistance below 8 units. All forty-four patients were considered good candidates for surgical intervention. Their ages ranged from three months to twenty-seven years. Fifteen of these patients were over ten years of age. The following clinical profile of the ideal candidate has been derived from the evaluation of these patients.

History: A cardiac murmur was noted during the first year of life in thirty of these forty-four patients. This, however, did not help differentiate this group of ideal patients from those with a small defect or from those with very high pulmonary vascular resistance. A history of easy fatigue, exertional dyspnea, or of heart failure, likewise, did not aid in separating these patients from those with very high pulmonary vascular resistance, who were relatively poor candidates for operative intervention. A history of recurrent infections of the upper respiratory tract and pneumonia in infancy or early childhood was found in twenty-four of the forty-four patients. A similar history was uncommon in the other groups. At the time of investigation, twenty of these patients were asymptomatic, while the others complained of undue exertional dyspnea and easy fatiguability. Among the older children these symptoms were in no way incapacitating. Thus, there is nothing distinctive relative to the history and symptomatology of these patients. It is the course followed by any patient with increased pulmonary artery blood flow.

Physical Examination: These patients were for the most part poorly developed and fell below the 50th percentile on the standard growth charts. In general, the higher the pulmonary vascular resistance, the poorer the growth and development. A deformity of the thorax was noted in most of the patients with large shunts. There was an increase in the angle of Louis and in the anteroposterior diameter of the chest with retraction of the lower part of the anterior rib cage. This is in contrast to the unilateral left precordial bulge noted in patients with atrial septal defects. The brachial pulse was normal or of slightly decreased volume, which was in contrast with the increased precordial activity. The deep veins of the neck were unremarkable, showing no elevation of pressure and the components were for the most part normal, although on occasion the "a" wave was slightly prominent.

Inspection of the precordium revealed a hyperdynamic apical impulse in the fifth left intercostal space and lateral to the mid-clavicular line, in the area associated with left ventricular enlargement. A systolic pulsation also was noted frequently in the second and third intercostal spaces, close to the sternum. This reflected the dilatation and increased activity in the area of the main pulmonary artery. On palpation there was clear evidence of enlargement and increased activity in the area of the left ventricle since there was a diffuse and hyperdynamic type of impulse. This finding was notably absent in the presence of a high pulmonary vascular resistance when the precordium was less active. Patients with lesser pulmonary artery blood flows and near normal figures for pulmonary vascular resistance revealed smaller and less active hearts with the apical impulse near normal. Clinical evidence of an enlarged and active left ventricle indicated that the left-to-right shunt was considerable and suggested that the pulmonary vascular resistance was not unduly raised. Twenty-four of these patients revealed evidence of increased activity and force of both ventricles. The presence of a sustained lift along the lower left sternal border without concomitant evidence of increased left ventricular activity at the apex was found in only one of the forty-four patients. This finding suggested high pulmonary vascular

resistance and only slightly elevated pulmonary artery blood flow, indicating that the patient is a high risk candidate for surgical intervention.

A systolic thrill was felt along the left parasternal area in twenty-one patients. Only six of these had a systolic pressure in their pulmonary artery of over 80 per cent of the systemic arterial blood pressure. However, six patients without severe pulmonary hypertension had no palpable thrill. Moreover, a few patients with very high pulmonary resistances had a systolic thrill in this area and this was also an extremely common finding in patients with relatively small septal defects. A shock was palpable over the second left intercostal space, close to the sternal border, in all but six patients.

On auscultation a harsh systolic murmur was noted in all patients. It was maximal at a point between the second and fifth intercostal spaces at the left sternal border. However, in the majority of the patients, this murmur was of maximal intensity in the fourth left intercostal space and of grade 3 to 6 in intensity and louder in the fifth than in the second left intercostal space. Occasionally, the murmur was maximal in the third intercostal space. The possibility of a mild element of infundibular obstruction had then to be considered. Pulmonary hypertension was invariably present when the murmur was loudest in the second intercostal space. The murmur was less intense in these patients, being grade 2 to 3 in intensity. The pulmonary component of the second heart sound was accentuated in all except six patients and four of these had little or no increase in pulmonary artery pressure. The second heart sound at the left base was narrowly split in all instances. A high pitched, blowing diastolic murmur was audible over the pulmonary area and transmitted down the left sternal border in three of the patients with considerable pulmonary hypertension. A short, low pitched, mid-diastolic murmur was heard at the apex of fifteen patients. There appeared to be no correlation between the presence of this murmur and the volume of the shunt flow.

Electrocardiogram: The electrocardiogram showed abnormally tall P waves in five of the forty-four patients, suggesting right atrial hypertrophy. This finding, however, was observed frequently in patients with high pulmonary vascular resistance, who were considered less than ideal candidates or in whom surgery was believed to be contraindicated. P waves of this configuration were not noted in patients

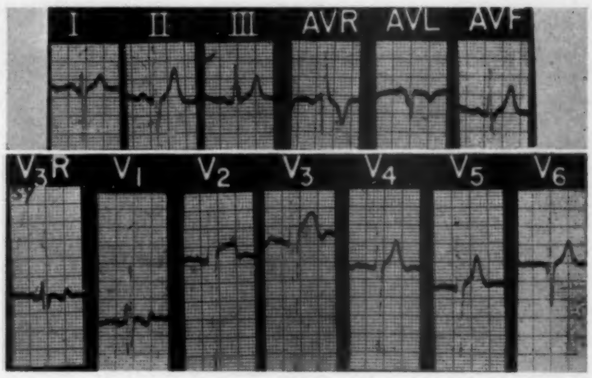


Fig. 1. Electrocardiographic evidence of biventricular enlargement and possible left atrial hypertrophy in a fourteen year old boy with pulmonary blood flow over three times systemic flow and mild pulmonary hypertension.

with small defects. The width of the P wave was more than 60 per cent of the P-R interval in twenty of the forty-four patients, suggesting that the left atrium was enlarged. Widening of the P wave in relation to the P-R segment was not observed in patients with severe elevation of pulmonary vascular resistance.

The mean electrical axis of the ventricular complex was normal (−30 to +100 degrees) in twenty-four of the forty-four patients. Left axis deviation (−30 to −120 degrees) with counterclockwise rotation, was present in eight patients in this group. Right axis deviation (+100 to −120 degrees) was noted in twelve patients and right bundle branch block was present in one patient of this latter group (Figs. 1 and 2).

Left ventricular hypertrophy alone was noted in fourteen patients while sole right ventricular

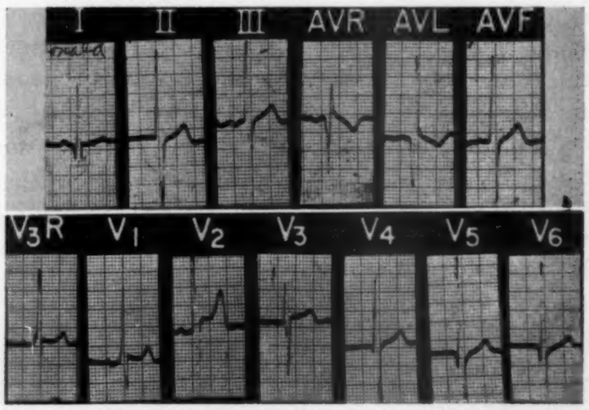


Fig. 2. Electrocardiographic evidence of biventricular enlargement in an eighteen year old boy with pulmonary flow over twice systemic flow and severe pulmonary hypertension. The patient is an ideal candidate for operation in spite of the considerable right ventricular enlargement and the pulmonary hypertension.

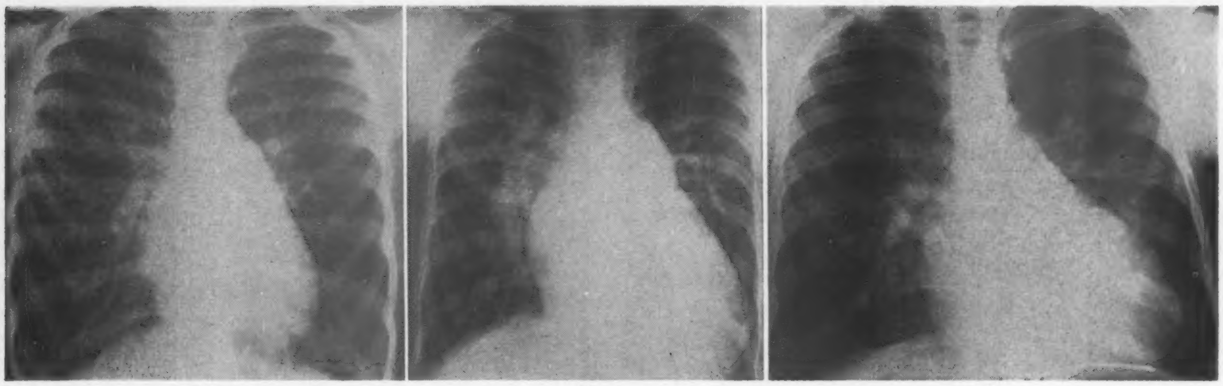


FIG. 3. Skiagrams of three ideal candidates for operation. There is a large variation in the shape of the hearts of these patients, but all show prominent pulmonary vascular markings. A, predominant right ventricular enlargement. B, predominant left ventricular enlargement. C, biventricular enlargement.

hypertrophy was found in seven, all of whom had considerable pulmonary hypertension. Evidence of combined left and right ventricular hypertrophy was present in twenty-two patients. One patient with left axis deviation had no definite evidence of enlargement of either ventricle. The height of the T wave in lead V_6 was over 5 mm. in twelve patients despite considerable pulmonary hypertension in four. The finding of left ventricular hypertrophy alone is relatively common in patients with a large left-to-right shunt. However, it was noted too often in association with considerable elevation of pulmonary vascular resistance (in the less than ideal candidates) to be of use in differentiating the individual case.

Radiologic Examination: Fluoroscopy and x-ray examination of the heart and lungs showed slight to marked cardiac enlargement in all patients (Fig. 3). The left atrium was slightly enlarged in most of these patients and this was taken as evidence of a left-to-right shunt of considerable magnitude. The right ventricle was thought to be enlarged in all patients with significant pulmonary hypertension. The assessment of additional left ventricular enlargement was difficult. When this could be accomplished, it was helpful, as the left ventricle was not enlarged in children with a very high pulmonary vascular resistance.

The main pulmonary artery appeared prominent in all children and adults, but in two infants appeared to be of normal contour. The right and left pulmonary arteries were increased in size and the peripheral pulmonary arterial branches appeared to be enlarged well out toward the periphery of the lung. An increase in the amplitude of pulsation of these vessels was also noted. This last finding provided additional evidence for a considerable left-to-right shunt. The pulmonary arterial resistance was invariably elevated when there was disparity between the size of the hilar and peripheral branches of the pulmonary artery. The aorta was unremarkable in size and activity or pulsation in these patients. The presence of a patent ductus arteriosus as an additional defect is strongly suggested by a large, actively pulsating aortic arch.

Physiologic Data: Cardiac catheterization must confirm that the left-to-right shunt occurs at the ventricular level and also provide data for estimating the relative flows and resistances in the two great vessels. Samples of right ventricular and pulmonary arterial blood contain a higher saturation of oxygen than do samples from the right atrium. However, passage of the catheter through the defect is uncommon. The pulmonary and systemic arterial pressures should be measured at the time of the studies of cardiac output at rest.

The ratio between the differences in pulmonary and systemic arteriovenous oxygen saturation is the same as the ratio between the pulmonary and systemic flows. The pulmonary arteriovenous oxygen difference is narrow when the shunt is large, and a small error in this measurement would produce a significant error in the estimate of the pulmonary blood flow. Knowledge of the exact volume of a large shunt is not important since closure of the defect is always advisable. When the pulmonary flow is close to the critical level of twice the systemic flow, the arteriovenous oxygen difference is larger and a similar error is less significant in the calculation of flow.

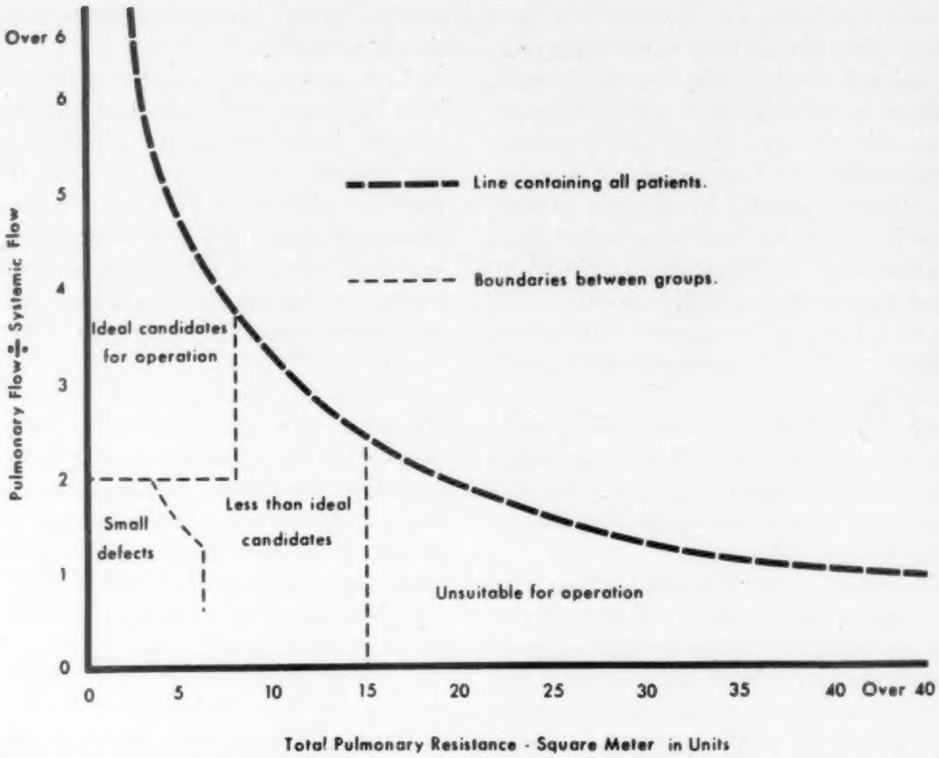


Fig. 4. The separation of patients into different groups allowing proper surgical selection, based on relation between pulmonary resistance and relative flows.

The pulmonary index is estimated by dividing the pulmonary blood flow in liters per minute by the surface area in square meters. The total pulmonary arterial resistance corrected for body surface area (TPR/M^2) is obtained by dividing the mean pulmonary arterial pressure in millimeters of mercury by the pulmonary index. The result is expressed in units of resistance (1 unit = 80.004 dynes sec. $cm.^{-5}$).

Even an error as large as 25 per cent in the estimation of the TPR/M^2 can only affect the choice of patients for surgery when the result is between 8 and 18 units. Errors can be reduced by repeating the sampling, pressure recording and uptake of oxygen necessary for this calculation. The data obtained from these studies must not be accepted too rigidly and a small allowance for possible errors is advisable. The interpretation of physiologic data should always be correlated with the clinical evaluation of the volume of the pulmonary artery blood flow.

The systemic index is normal in the majority of patients, so that a ratio between the pulmonary and systemic flows is a useful method of comparing shunts in different patients. The pulmonary artery pressure may rise considerably with a large pulmonary blood flow when the resistance to flow is but slightly elevated. This has been termed *hyperkinetic pulmonary hypertension.*[10] Such patients are ideal candidates for operation, since closure of the septal defect will reduce the pulmonary blood pressure to normal or near normal levels.

A small elevation in TPR/M^2 (5 to 7 units) can be due to increased left atrial pressure which may be present with large volume left-to-right shunts, but moderate elevation implies an obstruction to blood flow in the pulmonary vascular bed. If the resistance is labile under the influence of drugs or the inhalation of oxygen, the accompanying pulmonary hypertension is termed *vasoconstrictive or reactive.* The pulmonary hypertension is probably due to obliterative pulmonary vascular disease when the raised TPR/M^2 cannot be lowered, and extensive intimal fibrous changes of the small pulmonary arteries should be suspected.

The physiologic data have been analyzed from 133 of our patients who have had adequate cardiac catheterization. The relation between the pulmonary resistance and the relative flows has been plotted (Fig. 4). All our patients fell below or to the left of the containing line. Patients have been grouped by arbitrarily placing boundary lines on the graph. As already men-

tioned, *the ideal candidates for operation are those with a pulmonary flow at least twice the systemic flow, and a total pulmonary resistance not exceeding 8 units.*

Small defects were diagnosed when the pulmonary flow was less than twice the systemic flow, and the resistance was less than 6 units. *Whenever the resistance exceeded 15 units, the patients were considered unsuitable for surgery,* although it is possible that this view may become modified in infants. The intermediate group is made up of patients who are suitable for surgery only when there is evidence that this increased pulmonary resistance is labile.

The boundaries are placed as we believe they should be at the present time. With increasing knowledge it is hoped that the boundaries containing candidates suitable for operation will be moved further to the right.

Severe pulmonary hypertension with a systolic pressure approaching that in the aorta is not necessarily a contraindication to operation, since the pulmonary resistance will only be near the upper limit of normal when the pulmonary index is large. A relatively small pulmonary index with severe pulmonary hypertension indicates raised total pulmonary resistance. The level of the resistance is far more important than the pulmonary arterial pressure in deciding on operability.

Pathology of Pulmonary Vessels: The appearance of the small pulmonary arteries and arterioles has been examined microscopically by Dammann and Ferencz[11] and the degree of changes has been graded according to severity by Heath and Edwards.[12]

Hypertrophy of the muscle in the media is noted in all grades. In grade 1 the intima is normal, but cellular proliferation is present in grade 2. Early fibrous changes in the intima and slight generalized dilatation of the arteries are found in grade 3. The characteristic lesions in grade 4 are the localized plexiform dilatations. Chronically dilated vessels with fibrosis of the media and pulmonary hemosiderosis or necrotizing arteritis are the most severe changes seen and are graded 5 and 6 respectively.

There is close correlation between the age of the patient and the severity of the lesion, indicating that these changes take time to develop. Following closure of the ventricular septal defect an immediate fall in pulmonary artery pressure to near normal levels has been noted in patients with grade 1 to 3 changes while most patients with grade 4 showed a moderate reduction in pulmonary hypertension, and no fall in pulmonary artery pressure occurred in patients with grade 5 changes.[13]

This evidence supports our interpretation that lability of the pulmonary artery pressure is usually found when the elevated resistance is due mainly to hypertrophy of the muscular media. This is more common in infants and young children than in adults. When the cross-sectional area of the vessel is reduced significantly as the result of marked intimal fibrosis and thrombosis, the elevated resistance tends to be fixed.

Ten of our patients who underwent surgical closure of a ventricular septal defect have had portions of their lungs examined and the changes present have been graded as described. All of these patients have had changes characteristic of one of the first three grades and the pulmonary vascular resistance and pressure have fallen significantly in all patients.

Less Than Ideal Candidates for Surgery

Patients falling into this category have pulmonary artery blood flows that are slightly elevated, being less than twice the systemic blood flow. The total pulmonary vascular resistance varies considerably in this group. Some patients have normal or only slightly elevated pulmonary vascular resistance. They are considered to have relatively small defects and operation is not deemed advisable at this time.

Others will have moderate to markedly elevated pulmonary vascular resistance. These patients are thought to have large defects and the level of their pulmonary vascular resistance approaches or equals their systemic resistance, which accounts for the paucity of their shunt flow. They are not automatically excluded from consideration for surgical intervention, but they present a high risk and must be evaluated more carefully.

The prime consideration in the selection of patients from this group for operation is the lability of resistance in the pulmonary vascular bed. The elevated TPR/M^2 is due mainly to increased obstruction to flow in the small pulmonary arteries. If these changes are permanent, then closure of the septal defect will not effect a cure and the operative risk will be high. The reduction in pulmonary flow can be only relatively small but moderately severe pulmonary hypertension will persist. In the immediate postoperative period there is great risk of right ventricular failure. If they survive surgery, it seems likely that the

TABLE I
Physiologic Studies on Patient M. E.

Status	Oxygen Saturation (Per Cent)				Pressure (mm. Hg)				Flow (L./min.)				Units of Resistance		
	Right Atrium	Right Ventricle	Pulmonary Artery	Systemic Artery	Right Atrium	Right Ventricle	Pulmonary Artery	Systemic Artery	Pulmonary Flow	Pulmonary Index	Systemic Flow	Systemic Index	TPR	TPR/M^2	Total Systemic Resistance/M^2
July 1952; age four months															
At rest	59	74	73	...	2	95/0	95/55	...	...	...	...	...	...	...	...
April 8, 1957; age five years															
At rest	58	73	71	81	3	104/6	104/62	110/65	3.4	5.5	3.2	5.2	22	14	15
After Priscoline	...	...	85	92	...	...	70/40	98/57	13.3	21.5	...	...	4	2	...
June 6, 1958; age six years															
At rest	64	64	64	87	2	48/2	48/18	114/70	3.4	4.5	3.4	4.5	8	6	19
After Priscoline	...	...	64	85	...	...	30/10	112/75	4.4	5.7	...	...	4	3	...

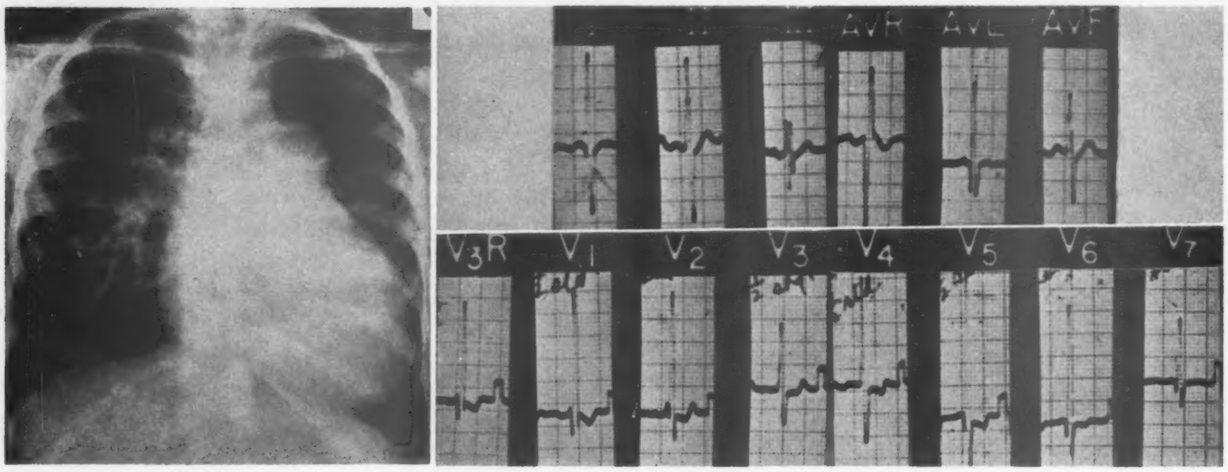
course that these patients would follow would be similar to that observed in primary pulmonary hypertension. On the other hand, when the increased resistance in the small pulmonary arteries regresses with closure of the defect, then the pulmonary artery pressure and flow become normal and a complete correction has been achieved.

Determination of Lability of Pulmonary Vascular Resistance: It is necessary to decide that an increased pulmonary resistance is labile to some extent before advising operation. After the resistance has been estimated at rest, a drug or gas capable of reducing the resistance may be administered, and the procedure repeated. For this purpose injections of acetylcholine, aminophylline or Priscoline® and inhalation of 100 per cent oxygen have been used. In our laboratory Priscoline has been selected as the most suitable agent since its action is selectively on the pulmonary vascular bed. The systemic circulation is affected only transiently and systemic resistance and left atrial pressure are not significantly changed at the time of estimating the response of the pulmonary resistance to Priscoline.

The technic used is as follows:[14] After the usual sampling and measurements of pressure at rest are completed, an injection of Priscoline (1 mg. per kg. body weight) is made through the catheter directly into the pulmonary artery. Ten minutes later the pulmonary and systemic flows are again measured and the pulmonary artery pressure recorded. If the TPR/M^2 falls to a level of less than 6 units then the increased resistance is thought to be in part due to vasoconstriction and the patient is considered as a suitable candidate for surgery.

In our laboratory this fall in pulmonary resistance following the injection of Priscoline is commonly seen in infants and young children. No significant reduction has been observed in any patient aged twelve years or more. It may be that changes in the pulmonary vascular bed have become irreversible before this age and, as a result, it appears that the investigation and treatment of patients with raised pulmonary resistance should be carried out in early childhood whenever possible. It is important to appreciate that a loss of lability is not necessarily associated with an increase in pulmonary resistance during childhood.

Illustrative Case: As an example of this problem the following patient is presented. M. E., a five year old white female, was the product of a normal pregnancy and delivery. A heart murmur was noted for the first time at four months of age. At that time cardiac catheterization was performed at another hospital. Evidence of a small left-to-right shunt at the ventricular level was found. The pressure in the pulmonary artery was 95/55 mm. Hg (Table I). Before the age of five she had pneumonia on six occasions



A B

FIG. 5. Skiagram (A) and electrocardiogram (B) in patient M. E. The chest leads are at half standardization. There is enlargement of both ventricles and the main pulmonary artery and its branches.

and it was noted that mild to moderate impairment of tolerance to exercise was present. She had never had cyanosis or revealed evidence of congestive heart failure.

On physical examination, the patient was small and thin and below the 10th percentile in both height and weight. There was no cyanosis, clubbing or edema. The peripheral pulses were full; blood pressure was 112/75 mm. Hg. The left precordium was prominent with increased activity over the entire cardiac area. There was a palpable lift over the right outflow tract. Left ventricular activity was increased in the left mid-axillary line. On auscultation, there was a rough, grade 2/6, systolic murmur maximal in the fourth left parasternal area, and a soft mid-diastolic apical murmur. The second heart sound was greatly accentuated and considered to be single.

Fluoroscopy revealed a considerably enlarged heart (Fig. 5A). The main pulmonary artery was prominent and the pulmonary vasculature was greatly increased. Both ventricles appeared enlarged. The *electrocardiogram* showed evidence of combined ventricular hypertrophy (Fig. 5B).

Cardiac catheterization before surgery revealed a relatively small bidirectional shunt at the ventricular level, severe pulmonary hypertension nearly equal to the systemic pressure and a considerable increase in total pulmonary resistance (Table I). After injection of Priscoline, these dynamics altered markedly. A large left-to-right shunt developed and the pulmonary resistance fell to a normal level.

On April 11, 1957 the patient's defect was closed with the aid of a pump oxygenator. The defect measured 4 by 2 cm. Postoperatively mild cardiac decompensation developed but she responded well to treatment. Since then her tolerance to exercise has increased markedly and she is now entirely free of symptoms.

Cardiac catheterization was repeated on June 6, 1958 (Table I). It will be noted that her pulmonary vascular resistance has decreased considerably from the preoperative level and is now only slightly elevated. Mild residual pulmonary hypertension was shown and this may continue to regress.

Comment: Before operation the cardiac catheterization studies showed that there was only a small left-to-right shunt and a definite right-to-left shunt as manifested by significant arterial desaturation at rest. The severe pulmonary hypertension and the high pulmonary resistance might have been considered to preclude surgery. However, the low systemic resistance explained in part the paucity of the left-to-right shunt and the dramatic response to the effect of Priscoline suggested that the elevated pulmonary vascular resistance was due to vasoconstriction and not to obliterative disease.

Patients who are now considered inoperable because of a high total pulmonary resistance may be correctible eventually. It seems possible that changes in the small pulmonary arteries might regress if the defects are closed or the main pulmonary artery banded in infancy or early childhood.

More data are needed on the correlation between the effects of closure of the septal defect and of injection of Priscoline on the total pulmonary resistance. It may be found that extensive irreversible changes in the pulmonary arterial bed develop earliest in those with the highest resistances.

SUMMARY AND CONCLUSION

An understanding of the natural history of patients with a ventricular septal defect is essential in their evaluation and in consideration

of surgical treatment of the defect. This understanding is still incomplete at the present time, and current concepts may change as additional experience is gained.

At this time the ideal patient for surgical intervention is believed to have a defect resulting in a large volume of shunt with a high pulmonary arterial blood flow and normal or only slightly elevated pulmonary vascular resistance. Successful closure of the defect will assure reduction of the work of the heart to normal or near normal and arrest the trauma to the pulmonary vasculature. This is accomplished by the return of the output of the left ventricle and the reduction of the pulmonary artery blood flow and pressure to normal.

Patients with mildly elevated pulmonary arterial blood pressure and flow and normal pulmonary vascular resistance are considered to have small defects. These patients are not considered candidates for surgery at the present time, because the risk of surgery is still relatively high and the prognosis for this group of patients is good. It is appreciated that in the not too distant future, operation will be advised in all patients with a normal pulmonary resistance and as currently practiced in patients with patent ductus arteriosus and atrial septal defect the indication for operation will be the diagnosis of the defect. Emphasis is placed upon the belief that there is rarely an emergency relative to surgery between the ages of two and ten years when the level of the pulmonary resistance is normal.

The less than ideal candidate has been evaluated and stress has been placed on the importance of the pulmonary vascular resistance rather than the pulmonary arterial blood pressure in the selection of patients for surgery. Also, the need for knowledge of the lability of the pulmonary arterial resistance as demonstrated by a fall in resistance following administration of Priscoline has been emphasized in the evaluation for surgery of the less than ideal candidate.

At the present time the patient with considerable or severe elevation of pulmonary vascular resistance and no evidence of lability is considered to be a poor candidate for operation. Certainly, in this group of patients, the risk of operation is high and the gain that may be expected is minimal.

References

1. Blount, S. G., Jr., Mueller, H. and McCord, M. C. Ventricular septal defect. Clinical and hemodynamic studies. *Am. J. Med.*, 18: 871, 1955.
2. Abbott, M. E. Statistics of congenital cardiac disease (1000 cases analysed). Reprinted in: Disorders of the Heart and Circulation. Edited by Levy, R. L. New York, 1951. Thomas Nelson and Sons.
3. Engle, M. A. Ventricular septal defect in infancy. *Pediatrics*, 14: 16, 1954.
4. Edwards, J. E. Symposium on cardiovascular diseases; functional pathology of congenital cardiac disease. *Pediat. Clin. North America*, 1: 13, 1954.
5. Zacharioudakis, S. C., Terplan, K. and Lambert, E. C. Ventricular septal defects in the infant age group. *Circulation*, 16: 374, 1957.
6. Muller, W. H., Jr. and Dammann, J. F., Jr. The treatment of certain congenital malformations of the heart by the creation of pulmonic stenosis to reduce pulmonary hypertension and excessive pulmonary blood flow: a preliminary report. *Surg., Gynec. & Obst.*, 95: 213, 1952.
7. Fyler, D. C., Rudolph, A. M., Wittenborg, M. H. and Nadas, A. S. Ventricular septal defect in infants and children. A correlation of clinical, physiologic and autopsy data. *Circulation*, 18: 833, 1958.
8. Weinberg, M., Fell, E. H., Gordon, A. S., Gasul, B. M., Lynfield, J., Luan, L. and Johnson, F. R. The natural course of infants and children with ventricular septal defects. *S. Forum*, 9: 291, 1958.
9. Kjellberg, S. R., Mannheimer, E., Rhude, U. and Jonsson, B. Diagnosis of Congenital Heart Disease. Chicago, 1955. Year Book Publishers, Inc.
10. Wood, P. Diseases of the Heart and Circulation, 2nd ed. London, 1956. Eyre & Spottiswoode.
11. Dammann, J. F., Jr. and Ferencz, C. The significance of the pulmonary vascular bed in congenital heart disease. III. Defects between the ventricles or great vessels in which both increased pressure and blood flow may act upon the lungs and in which there is a common ejectile force. *Am. Heart J.*, 52: 210, 1956.
12. Heath, D. and Edwards, J. E. The pathology of hypertensive pulmonary vascular disease. A description of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects. *Circulation*, 18: 533, 1958.
13. Heath, D., Helmholz, F., Burchell, H. B., DuShane, J. W., Kirklin, J. W. and Edwards, J. E. Relation between structural changes in the small pulmonary arteries and the immediate reversibility of pulmonary hypertension following closure of ventricular and atrial septal defects. *Circulation*, 18: 1167, 1958.
14. Grover, R. F., Bowes, W. A., Jr. and Blount, S. G., Jr. Pulmonary hypertension relieved by Priscoline in patients with congenital heart disease. Presented to the Western Society for Clinical Research, Carmel, California, January 30, 1958.

Surgical Treatment of Ventricular Septal Defects*

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THE surgical treatment of ventricular septal defect by open technics has been practiced for nearly six years. In 1955, Lillehei and associates[1] reported their first cases in which operation was performed with the aid of controlled cross circulation. In 1956 the early cases in which a mechanical pump-oxygenator was used were reported by DuShane et al.[2]

Since that time, sufficient experience has accumulated to allow the conclusion that operation is an effective treatment for patients with ventricular septal defect. Although some difference of opinion continues to exist with regard to the selection of patients for operation, data are being accumulated which should result in final agreement on this point. Surgical technics will probably continue to vary for a long time. Nonetheless, certain basic requirements of a successful technic have become clear. The results of operation have been, by and large, good. Complications, notably the development of complete heart block and the persistence of residual shunt, continue to occur, but only in a small percentage of patients.

It can be said, then, that the surgical treatment of ventricular septal defect has now taken its place among the well accepted and well documented procedures in surgery.

INDICATIONS FOR OPERATION

Once the diagnosis of ventricular septal defect has been made, a decision for or against operation is necessary. Some patients with ventricular septal defect have a harsh precordial systolic murmur as the only clinical manifestation of their condition. The heart is not overactive and no apical diastolic inflow murmur is found. The thoracic roentgenogram in such patients reveals little, if any, increase in pulmonary vascularity and the cardiac silhouette is within normal limits. The electrocardiographic findings in such patients are also within normal limits. If cardiac catheterization is carried out, the data reveal normal pulmonary artery pressure and only a small increase of pulmonary over systemic blood flow. Although it is undoubtedly true that these patients can be operated on with a hospital mortality rate of less than 5 per cent, it has not been our practice to advise operation under these circumstances unless the patient has had subacute bacterial endocarditis. The patient should be examined at yearly intervals in order to be certain that the condition has not progressed. It is freely admitted that the time may come when operation will be advised for such patients.

We consider all patients with clinical evidence of hemodynamic derangement from the ventricular septal defect for operation. Overactivity of the heart, an apical diastolic inflow murmur, electrocardiographic abnormalities, significant degrees of left-to-right shunting and pulmonary hypertension demand an evaluation of the patient for possible operation.

Pulmonary Hypertension and Relation of Pulmonary to Systemic Blood Flow: When pulmonary artery pressure is definitely less than aortic pressure, one can be sure that the patient is operable. Under these circumstances, pulmonary flow is in excess of systemic flow. When pulmonary artery and aortic pressures are nearly identical, the decision for or against operation cannot be based on measurement of pulmonary artery pressure alone.

As background to this it must be noted that as a result of a large experience in the surgical treatment of atrial septal defect, ventricular septal defect and patent ductus arteriosus, we have developed a basic concept of operability in patients with congenital malformations allowing

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shunting between the pulmonary and systemic circulations and with severe pulmonary hypertension. The basic considerations in the development of this concept have been reviewed elsewhere.[3] In brief, the evidence to date indicates that operation is not of value to patients with such malformations and with severe elevation of pulmonary artery pressure if it does not result in at least some fall in this pressure after operation. In our experience, late reduction in pulmonary artery pressure has not been seen unless there was some immediate fall in this pressure relative to systemic pressure following repair. Whether closure of the defect is abrupt or gradual, such a fall in pulmonary artery pressure relative to systemic pressure cannot occur unless prior to repair pulmonary flow was in fact in excess of systemic flow. Thus, it can be seen that the emphasis must be on the response of the pulmonary artery pressure to repair rather than on the absolute level of the pressure prior to operation. The response of pulmonary artery pressure to repair can be predicted if there is knowledge of the relation of pulmonary to systemic blood flow prior to operation.

Thus, in patients in whom pulmonary hypertension is so severe that pulmonary artery and aortic pressures are nearly identical, operation is believed advisable when pulmonary flow remains in excess of systemic flow. Although the concept is clear, the decision in the individual patient as to the relative magnitudes of pulmonary and systemic flow and thus as to the patient's operability may remain difficult. When marked cardiac enlargement, hyperemia of the lungs and clear left ventricular overload evidenced by electrocardiogram are present, it is apparent that pulmonary blood flow is large relative to systemic flow and that operation is indicated. When the patient with ventricular septal defect and pulmonary artery hypertension has cyanosis and the pulmonary fields are anemic, as determined roentgenographically, and when the heart shows no evidence of left ventricular enlargement and only striking right ventricular hypertrophy, it is clear that the shunt is predominantly right to left, that pulmonary flow is less than systemic flow and that operation is contraindicated. In borderline cases, however, a decision may be extremely difficult even with the aid of complete hemodynamic data. Under such circumstances we have usually advised operation, recognizing the imponderables thereof.

Surgery in Infancy: Infants with ventricular septal defect can be operated on with reasonable safety. Yet, it has appeared wise to defer operation until the age of two or three years when the child is doing well. Infants in whom cardiac failure persists in spite of adequate medical treatment should be treated by open intracardiac repair. The hospital mortality rate of 23 per cent in this group is higher than that in older patients, but acceptance of this risk appears preferable to accepting the higher risk of continuing medical treatment under these circumstances.

Surgical Technics

Whole body perfusion with the use of the pump-oxygenator is, at present, the method of choice for approach to the repair of ventricular septal defect. At the Mayo Clinic experience with open intracardiac operations utilizing extracorporeal circulation in 975 patients has yielded convincing evidence as to the safety of this technic under proper circumstances. However, other technics are appearing which may rise to challenge whole body perfusion in the future. Most noteworthy is the recent experience of Drew and Anderson[4] utilizing profound hypothermia and circulatory arrest induced by extracorporeal circulation without the use of an artificial oxygenator.

Induced Cardiac Asystole: Difference of opinion continues among surgeons as to the wisdom of repairing ventricular septal defect under conditions of induced cardiac asystole. Some surgeons prefer to make the repair without inducing asystole, because of the fear that the necessary cessation of coronary blood flow may be severely deleterious to the heart. Likewise, some prefer to avoid asystole in order that heart block may be identified should it occur as a suture is being placed.

My associates and I continue to prefer to repair ventricular septal defects with the aid of induced cardiac asystole. Our original experience with asystole induced with potassium by the Melrose technic seemed clinically satisfactory. However, for the last twelve months asystole has been induced by simple anoxia and cross clamping of the aorta. In spite of the theoretical objections that have been properly raised to this technic, in clinical practice we have not as yet identified with certainty any deleterious effects. It appears that the technical advantages gained from working within the quiet, relatively bloodless ventricle outweigh the theoretical disadvantages in the use of asystole.

FIG. 1. Autopsy specimen of the heart of a patient who died after repair of a large, high ventricular septal defect. The septum is viewed from the left ventricular aspect. The suture line, parallel to and immediately beneath the aortic annulus, is barely visible.

Technic of Closure of Defect: A difference of opinion likewise exists concerning the proper technic of closure of ventricular septal defect. Although in our early experience we preferred the use of a prosthesis in repair of such defects, we have tended to avoid it except under unusual circumstances in the last eighteen months. The experience with repair of most of these defects by direct suture has been highly satisfactory and thus continues to be for us the method of choice (Fig. 1). Particular care must be utilized in placing the sutures to avoid the region usually occupied by the main bundle of His.

POSTOPERATIVE CARE

The management of patients subjected to open intracardiac operation with the aid of extracorporeal circulation has recently been detailed by Lyons and co-workers.[5] Certain features of the care of patients with repair of ventricular septal defect are reviewed here.

In general, it is thought that few special measures are necessary in the postoperative period if the operation has been accurately accomplished in all details. It is extremely rare that tracheotomy or assisted ventilation is utilized. No special monitoring devices are employed in the postoperative period save for an occasional case in which the electrocardiogram is continually monitored on an oscilloscope. Venous and arterial blood pressures are not monitored through indwelling needles. Rather, venous pressure is estimated clinically by observation of the veins of the neck, and arterial pressure is taken by the usual cuff method. In infants, the efficacy of the circulation in the early postoperative period is estimated by palpation of the radial pulse.

Patients are returned from the operating room to a special cardiovascular unit where they are placed in bed and in an atmosphere that is heavily humidified and contains about 50 per cent oxygen. Thoracic tubes are attached to a source of gentle negative pressure, and the amount of blood emerging from the thorax is carefully recorded. This blood is accurately replaced, but the amounts involved are usually small.

Fluids: All fluid is given intravenously in the form of a 5 per cent solution of dextrose and distilled water for the first forty-eight hours after operation. On the day of operation, fluid is given in an amount of 500 cc. per square meter of body surface per twenty-four hours. On the following two days it is given in the amount of 750 cc. per square meter per twenty-four hours. Thereafter, patients are allowed to take fluids and food by mouth.

Heart Block: If complete heart block has developed in the operating room, a myocardial stimulating wire is left in place and an artificial pacemaker is used for forty-eight to seventy-two hours. If by this time sinus rhythm has not supervened, the patient is weaned away from the pacemaker, if necessary with the use of isoproterenol (Isuprel®) hydrochloride given rectally in doses of approximately 5 mg. every two to four hours. Details of the management of these patients have recently been published.[6]

Digitalization: In patients with severe pulmonary hypertension in whom the pulmonary artery pressure falls only slightly immediately after repair, digitalization on the day of operation is usually felt to be advisable. Likewise, severe tachycardia, hypotension in spite of adequate blood replacement or undue elevation of venous pressure as estimated by the appearance of the veins of the neck is considered to be an indication for prompt digitalization. However, unless a clear indication for the administra-

tion of the drug is present, it is preferred to avoid its use in the first four to five days after operation because of the clinical impression that heart block can be produced in these patients with doses of digitalis that under ordinary circumstances would not be considered toxic.

The keystones of postoperative care are an adequate operation, an adequate perfusion and careful observation of the patient in the period after operation.

Heart Block Following Repair of Ventricular Septal Defect

The subject of the development of complete heart block following repair of ventricular septal defect has recently been thoroughly reviewed by Lauer et al.[6] This study showed that with the present technic that is employed for direct suture at the Mayo Clinic the incidence of complete and permanent heart block is 5 per cent. There is a somewhat higher incidence of patients showing complete heart block at some time during the postoperative period. In many instances, however, the heart block is temporary and sinus rhythm supervenes and remains permanently.

At present, complete heart block occurs infrequently as a permanent complication of the operation, but when it does occur, treatment must be adequate and the patient must be carefully followed up for a long time. On occasions these patients have symptoms of syncope and Stokes-Adams episodes for many months following operation and require the use of isoproterenol to maintain the heart rate at a level where symptoms will not occur. Late death is always a threat in patients with this complication. Yet, some have now survived for a long period after operation and appear destined to remain well in spite of the persistence of a slow ventricular rate.

Because of these facts it is believed that every effort must be made to avoid the production of complete heart block in the repair of ventricular septal defect. The experience of the last eighteen months has indicated that the incidence of this complication can be low. Complete prevention of the complication is the goal to which surgery must aspire.

Residual Shunt at Ventricular Level

In a report in 1957 on our early experience with ventricular septal defect, the problem of residual shunt after the operation was discussed.[7] Few data on the subject are available in the literature. The cause of residual shunting at ventricular level may be an overlooked second ventricular septal defect, a recurrence of a previously completely closed defect or the persistence and enlargement of a very small residual shunt present immediately after repair.

In every patient, careful search of the entire ventricular septum must be made in order to be certain that an additional defect is not overlooked. Recurrence of ventricular septal defects after previously complete repairs sometimes takes place. In our own experience, however, there have been only two documented cases. In both, the ventricular septal defect had been repaired with compressed polyvinyl (Ivalon®) sponge.

Although sufficient data are not yet available from our own experience to know with certainty the incidence of persistent shunt following repair by direct suture, it appears to be less than 10 per cent. The defect is always carefully inspected with the heart beating before closing the ventricular incision. Yet, in a few cases, a soft systolic thrill over the outflow tract of the right ventricle or in the pulmonary artery did develop shortly after the patient's heart took over the circulation. A somewhat harsh systolic murmur could be heard late in the day of operation. For these reasons it is believed that this small group of patients who show significant shunting at the ventricular level sometime after repair of ventricular septal defect have it on the basis of a very small residual shunt that is present shortly after the heart has been restarted and that enlarges in the days thereafter.

Results of Surgery

The hospital mortality rate in the first twenty patients with ventricular septal defect operated upon at the Mayo Clinic in 1955 was 20 per cent.[2] The corresponding rate for the period January 1 to October 1, 1959, is 5.4 per cent. Sixty per cent of the patients continue to be those with severe elevation of pulmonary artery pressure. On the basis of this experience it can be stated that ventricular septal defect can be repaired at an acceptably low hospital mortality rate.

The regression of pulmonary hypertension following repair of ventricular septal defect with severe pulmonary hypertension and large pulmonary blood flow has been dramatic and gratifying. Reduction in cardiac size and striking improvement in growth and general well-being are equally dramatic.

An over-all hospital mortality rate of approximately 5 per cent, an incidence of complete and permanent heart block of approximately 5 per cent and an incidence of residual shunting of approximately the same degree mar the general picture somewhat. It is to be recalled, however, that the hospital mortality rate and the incidence of complications are accounted for almost entirely by the patients with ventricular septal defect and severe elevation of pulmonary artery pressure. This does not suggest that the risk is unduly high in this group, but it does imply that in patients with only moderate pulmonary hypertension or with little or no pulmonary hypertension the chances of an excellent result without mortality and without complication are significantly greater than in the group as a whole.

Summary

The subject of the surgical treatment of ventricular septal defect is reviewed. Certain items await statistical documentation and certain concepts remain as yet not totally proved. Yet, after five years of surgical experience with the treatment of ventricular septal defect, it can be stated with confidence that operation can yield a high incidence of excellent results in properly selected patients.

References

1. Lillehei, C. W., Cohen, M., Warden, H. E., Ziegler, N. R. and Varco, R. L. The results of direct vision closure of ventricular septal defects in eight patients by means of controlled cross circulation. *Surg., Gynec. & Obst.*, 101: 446, 1955.
2. DuShane, J. W., Kirklin, J. W., Patrick, R. T., Donald, D. E., Terry, H. R., Jr., Burchell, H. B. and Wood, E. H. Ventricular septal defects with pulmonary hypertension: surgical treatment by means of a mechanical pump-oxygenator. *J. A. M. A.*, 160: 950, 1956.
3. DuShane, J. W. and Kirklin, J. W. Selection for surgery of patients with ventricular septal defect and pulmonary hypertension. *Circulation* (In press).
4. Drew, C. E. and Anderson, I. M. Profound hypothermia in cardiac surgery: report of three cases. *Lancet*, 1: 748, 1959.
5. Lyons, W. S., DuShane, J. W. and Kirklin, J. W. Postoperative care after whole-body perfusion and open intracardiac operations. Unpublished data.
6. Lauer, R. M., Ongley, P. A., DuShane, J. W. and Kirklin, J. W. Heart block occurring after repair of ventricular septal defect in children. Unpublished data.
7. Kirklin, J. W., Harshbarger, H. G., Donald, D. E. and Edwards, J. E. Surgical correction of ventricular septal defect: anatomic and technical considerations. *J. Thoracic Surg.*, 33: 45, 1957.

Results of Surgery for Ventricular Septal Defects*

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BEFORE the advent of the extracorporeal circulation, no efficient method of treatment could be offered to patients with defects of the ventricular septum; in spite of the large number of children born with ventricular septal defects only a small percentage reached their teens. Abbott estimated the average age at death to be 14.5 years.

The possibility of direct vision repair of this lesion has completely changed the patients' prognosis. Experience with intracardiac surgery and cardiopulmonary bypass is now extensive enough to permit the repair of ventricular septal defects with a very low mortality rate.

SERIES OF CASES

This report concerns the direct vision repair of pure ventricular septal defect in sixty-four patients, in 38 per cent of whom severe pulmonary hypertension complicated the picture. The patients ranged in age from eighteen months to thirty-six years, the majority being between four and twelve years of age. The over-all mortality in this series is nine per cent. Death has not occurred in patients whose pulmonary artery pressure was less than 70 per cent of the systemic blood pressure. Improvements in operative and postoperative management have markedly decreased the mortality in these cases. There have been no deaths among the last thirty-eight patients regardless of the degree of pulmonary hypertension.

PREOPERATIVE EVALUATION

Although the diagnosis of ventricular septal defect can usually be made by the examination of the patient, a careful preoperative evaluation is indispensable in order to eliminate the presence of associated lesions and to determine the degree of hemodynamic alterations such as amount of shunt flow, pulmonary artery pressure, direction of the shunt flow and the degree of cardiac enlargement. Electrocardiographic and roentgenologic examinations, as well as cardiac catheterization studies, were performed in all patients. Inhalation of 100 per cent oxygen and the administration of intravenous aminophyllin during cardiac catheterization have proved to be valuable tests to determine the degree of fixation of the pulmonary pressure and resistance in patients with pulmonary hypertension and also offer a physiologic basis for the postoperative management of these patients. In a few patients the diagnosis was confirmed by cineangiocardiography.

In our opinion, all patients having ventricular septal defect with left-to-right or bidirectional shunt should be operated on regardless of the degree of pulmonary hypertension. We feel that patients having cyanosis with ventricular septal defects and permanent right-to-left shunt (Eisenmenger's complex) should not be subjected to surgery.

SURGICAL TREATMENT

APPROACH TO THE DEFECT

The approach to the heart was made initially through a bilateral thoracotomy incision with transection of the sternum. During the past year a longitudinal sternotomy has usually been employed. This gives excellent exposure to all aspects of the operative procedure and has many advantages over the bilateral thoracotomy incision, particularly relative to lessened postoperative pulmonary complications and to pain.

The extracorporeal circulation for all patients was provided by the Kay-Cross pump-oxygenator. One of the superficial femoral arteries was cannulated for the intake of the bypassed blood.

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The average perfusion rate varied from 50 to 70 cc. of blood per kg. in children and from 40 to 50 cc. per kg. in adults. Electrocardiograms and electroencephalograms were monitored continuously during the operation. The aortic and superior vena caval pressures were recorded constantly during the bypass. The oxygen tension of the arterial blood leaving the oxygenator was measured by a Clark oxygen polarograph and the carbon dioxide concentration of the effluent gases in the arterial end of the oxygenator was measured and recorded by a Beckman carbon dioxide infrared analyzer.

CLOSURE OF THE DEFECT

The simple suture of the ventricular septal defect has not been a good method of repair in our hands. A plastic patch (Ivalon® or Teflon®) was used to repair all ventricular septal defects. Exception was made in a few cases of very small defects of the membranous septum. The method of closure consisted of the placement of multiple interrupted silk sutures at the edges of the defect, followed by suturing of the patch. Small bites were taken in order to avoid including elements of the conduction system in the suture. Postoperative catheterization studies performed six months or more after surgery revealed that the defect was open in five patients. A second operation revealed that in three patients whose defect was closed by primary suture, the suture had torn out. In the other two, rupture of a non-compressed Ivalon patch was found to be the cause of the reopening of the defect. Since then a heavily compressed patch of Ivalon (16 to 1 mm.) has been used to avoid such a complication. The lesions of the five patients mentioned were completely repaired with the second operation.

ADVISABILITY OF CARDIAC ARREST

When the ventricular septum is exposed by cardiotomy, the continued heart beat often makes accurate identification and repair of the ventricular septal defect difficult or impossible. Although aware of increased danger of producing a permanent A-V block in motionless heart, elective cardiac arrest by the Melrose technic has been used in thirty-eight patients in this series. Potassium chloride (10 mEq. for children and 20 mEq. for adults) diluted in 50 cc. of arterial blood has been the cardioplegic agent of choice.

Ventricular fibrillation in the immediate postarrest period occurred in sixteen patients. Treatment consisted of the correction of hypotension, when present, with vasopressor agents, increasing coronary perfusion by increasing the perfusion rate, and the use of isoproterenol to change a "slow" type of fibrillation to a "fast" one, which could be treated more effectively by electric defibrillation. Special care was taken to avoid distension of the heart during the period of ventricular fibrillation. The above therapy has been effective in re-establishment of the normal heart beat in all patients with ventricular fibrillation after cardiac arrest.

COMPLETE A-V BLOCK FOLLOWING REPAIR OF DEFECT

Interference with the conduction system has not been a complication in this series. On two occasions, early in our experience, temporary A-V block appeared during the repair of the defect. The suture that produced the block was removed with immediate return to normal rhythm. When elective cardiac arrest was used, the sutures were placed carefully in order to avoid this complication. Although we know that, at the present time, this complication is managed successfully by the use of artificial pacemakers and isoproterenol, we believe that patients in whom this arrhythmia does not disappear will be handicapped markedly. The absence of this complication in our series has been a factor in the low rates of operative morbidity and mortality.

POSTOPERATIVE CARE

During the postoperative period special care was taken to maintain normal blood volume; otherwise the operation is poorly tolerated, particularly in patients with severe pulmonary hypertension. The airway was kept meticulously clear by tracheal aspiration with a laryngoscope. Only one tracheotomy was performed in the early part of our series. Periodically, artificial ventilation with a positive pressure respirator (Bennett) has been used during the postoperative period in patients with pulmonary hypertension. Intravenous aminophyllin has been administered after surgery in patients with severe pulmonary hypertension, with gratifying results.

Analysis of Results

Postoperative cardiac evaluation was performed six months to one year following surgery.

TABLE I
Hemodynamic Evaluation in Nine Patients with Ventricular Septal Defect and Pulmonary Hypertension

Patient	Pulmonary Artery Pressures (mm. Hg)		Shunt Flow (per cent)	
	Pre-operative	Post-operative	Pre-operative	Post-operative
J. L.	80/44	23/10	57	0
M. N.	75/40	31/6	50	0
J. McC.	72/35	30/13	70	0
R. P.	56/20	26/7	70	0
P. S.	78/24	46/12	70	0
P. R.	88/48	15/5	80	0
J. R.	67/32	19/10	48	0
D. S.	62/33	16/6	52	0
K. B.	98/52	47/33	55	0
Average	76.2/41	25/12.6	55.2	0

Analyzing the late results in sixty-four patients, we observed that the majority (five) of deaths occurred in the first eighteen months in which such operations were performed (January 1956 to July 1957). Since then only one death occurred. We believe that the improvement in operative and postoperative management secondary to the greater experience, as well as a better understanding of the underlying pathologic physiology, is responsible for this decrease in mortality. The clinical examination of patients at the time of discharge revealed that in the last two years all patients but one left the hospital without a heart murmur. Auscultation of the patient whose heart murmur persisted revealed that the murmur was softer and different in character than that heard preoperatively.

Postoperative cardiac catheterization revealed that the defects of five patients were open, as noted previously. Four of these patients were operated on in the period between January 1956 and July 1957. Reoperations have resulted in successful closure. The high incidence of complete closure in the last two years is due to the insistence upon a dry operative field and a complete identification of all characteristics of the defect. Elective cardiac arrest, when indicated, is used more frequently at present. The use of heavily compressed patches also has contributed to better repair of the defects.

Late evaluation in a group of nine patients with severe pulmonary hypertension revealed that six months or more after surgery the average drop in the pulmonary artery pressure was from 76.2/41 to 25/12.6 mm. Hg (Table I). The shunt flow was reduced from an average of 55.2 per cent to zero.

Summary

The surgical correction of ventricular septal defects can be accomplished today by teams experienced in extracorporeal perfusion technics with a minimum of risk and a maximum of effectiveness. There has been no operative mortality during the past two years in the series reported, regardless of the degree of pulmonary hypertension. With this degree of success it is believed that patients with significant shunt flows (40 per cent or more) should have the shunts closed without waiting for the development of enlarged hearts, increased pulmonary vascularity and pulmonary hypertension. Operative intervention is delayed in infants less than one year of age or less than 20 pounds in weight because of the increased risk.

Current Research in the Surgery of Ventricular Septal Defects*

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DEFINITIVE surgery for ventricular septal defects may be considered to have begun with first successful closure of such a defect under direct vision using cross-circulation with a human donor by Lillehei and his associates.[1] Previous attempts at "plugging" the defect[2,3] were for the most part incompletely effective and fundamentally unsatisfactory. Likewise the suggestion of Kay et al.[4] of inversion of the right ventricular wall against the septum, as the atrial wall can be inverted for the closure of atrial septal defects,[5] is inapplicable in the majority of instances.

Bailey[6] and Grow[7] and their associates were able to close a number of such defects using an open technic with the aid of hypothermia. Peirce et al.[8] reported successful closure of a traumatic septal defect using hypothermia. However, the period provided for the actual closure of the defect by establishment of general bodily hypothermia unfortunately is short, usually not more than seven minutes. This is insufficient for the correction of any but the simplest types of defect.

The successful closure by Kirklin et al.[9] of a ventricular septal defect under direct vision with the aid of extracorporeal bypass using a modified Gibbon[10] heart-lung apparatus has become the prototype of the modern surgical approach. Since then reports of sizeable numbers of such operations have appeared in the current literature.[11–13] On a theoretical basis this type of operation would seem to leave little to be desired. The early over-all surgical mortality, however, has been considerable, even disturbing, being of the order of 25 to 50 per cent. The reasons for this high fatality rate were multifold.

Initially a considerable portion of the mortality was attributable to the inherent risks of heart-lung bypass and the "open heart" technic, especially in their earlier and less completely perfected forms. Inseparable from this has been an avoidable increment of failure due to inexperience on the part of the surgeon, the clinician, and the anesthetist in the operative management of such cases.

A number of deaths have resulted from the inadvertent surgical interruption of the atrioventricular conduction system (bundle of His). This unfortunate complication has been largely due to incomplete understanding of the location and course of the bundle especially when dealing with these severely malformed hearts.

Perhaps the greatest single residual source of operative mortality in ventricular septal defect may be found in the improper selection of cases for definitive correction. Thus the surgical risk in tiny infants remains high; this is particularly true when dealing with unusually feeble subjects. However, the chief deficiency in selection is concerned with those who manifest significant pulmonary arterial hypertension and especially those who present a predominant right-to-left shunt through the defect.

An attempt will be made to highlight the efforts and measures which have been designed to reduce the number of fatalities which might be attributed to each of these medical and surgical shortcomings and to indicate the state of their present day effectiveness.

TECHNICS OF OPEN HEART SURGERY

Volumes have been written[14–17] on this subject and continuous modification, particularly in detail, may be expected for a long time. It does

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The research work basic to the development of this method of treatment was supported by the Mary Bailey Institute for Heart Research, Philadelphia, Pennsylvania.

not lie within the scope of this presentation either to review their development comprehensively or to foretell their probable final evolution.

The conventional complete heart-lung bypass entails the establishment of an extracorporeal circulatory system which comprises two pumps to replace the respective ventricles, an oxygenator to replace the lungs, and some type of filtration mechanism to prevent air bubbles and particulate matter from entering the arterial tree. It is customary practice at some clinics to eliminate the first (right ventricular) pump by the utilization of gravity drainage to divert the systemic venous return into the extracorporeal circuit.

PUMPS

The pumps employed are of several varieties. In general they may be divided into the continuous flow and the pulsatile flow types. The DeBakey roller type pump[18,19] and the Sigmamotor finger or peristaltic pump[20–22] are the most commonly used of the continuous-flow mechanisms. The Davol piston pump[23,24] may be considered to be representative of the pulsatile flow type. Initially these pumping mechanisms imparted serious measurable and presumably considerably less obvious damage, especially to the particulate elements of the blood. At the beginning, gross hemolysis often was demonstrable upon completion of the perfusion. Frequently this was manifested by persistence of a state of incoagulability of the blood or by renal shut-down. Progressive improvements in the pumping mechanisms, especially with respect to complete occlusion of the tubing, seemingly have reduced this source of blood trauma to a level which appears to be clinically negligible. The remaining major sources of blood damage now are related to the oxygenator, to the filtration mechanism, to the use of improper tubing or methods of cannulation, and especially to the "low pressure" suction devices which are used to keep the operative field dry.

OXYGENATORS

Oxygenators in present day use may be classified respectively as "bubbling," "filming" and "diffusing."

The bubble type oxygenator utilizes the blood-oxygen interface of numerous bubbles as a diffusing membrane through which oxygen may pass to combine with the reduced hemoglobin of the blood. Carbon dioxide is dispersed into the bubbles of gas and eliminated. Turbulence is

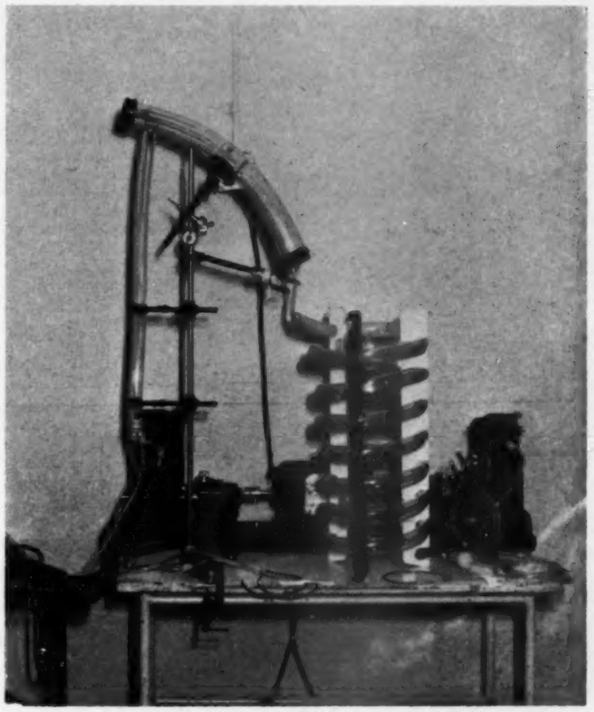


Fig. 1. Original DeWall bubble type oxygenator showing oxygenating tube (vertical), defoaming chamber (oblique) and settling helix.

inherent in the creation and transport of these bubbles and can lead to significant trauma to the particulate elements of the blood. The application of certain hydrodynamic principles, related especially to the gentleness of the introduction of the gaseous oxygen into the liquid blood, has reduced this source of trauma to a level which appears to be acceptable within the time limits entailed in the usual heart-lung bypass.

The bubble oxygenator has two significant advantages: (1) it can easily be designed to oxygenate a large quantity of blood per minute, and it eliminates any initial delay in establishment of oxygenation once the appropriate cannulations have been completed. However, there are two disadvantages inherent in this method of oxygenation. Inevitably some bubbles will remain floating upon, or (worse) mixed within the depths of, the oxygenated blood. These must be removed in some fashion lest they cause arterial air embolism. Effective combinations of methods of chemical coalescence of smaller bubbles into large ones (Dow Chemical's Anti-Foam), gravity separation and utilization of the deeper layers of blood, and methods of trapping bubbles floating upon the surface have been devised which when working properly act to keep this risk at a minimum (Fig. 1).

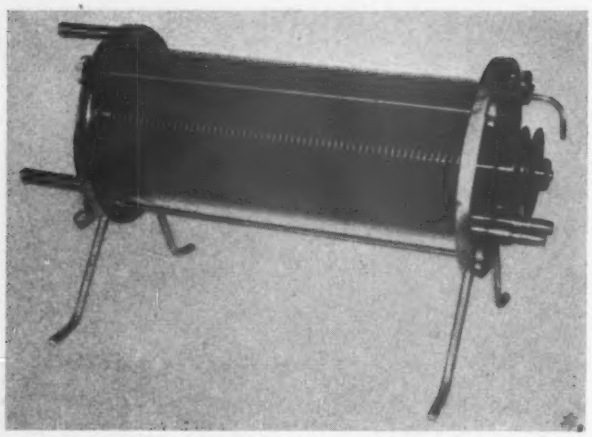


FIG. 2. Kay-Cross filming oxygenator which utilizes revolving discs.

An untoward and seemingly largely disregarded aspect of this method of oxygenation is the present necessity for applying 90 to 100 per cent (caustic) concentrations of pure oxygen directly to a blood surface. While this is clinically acceptable for the periods of time required for the usual cardiopulmonary bypass, it would seem restrictive to significant prolongation of this period.

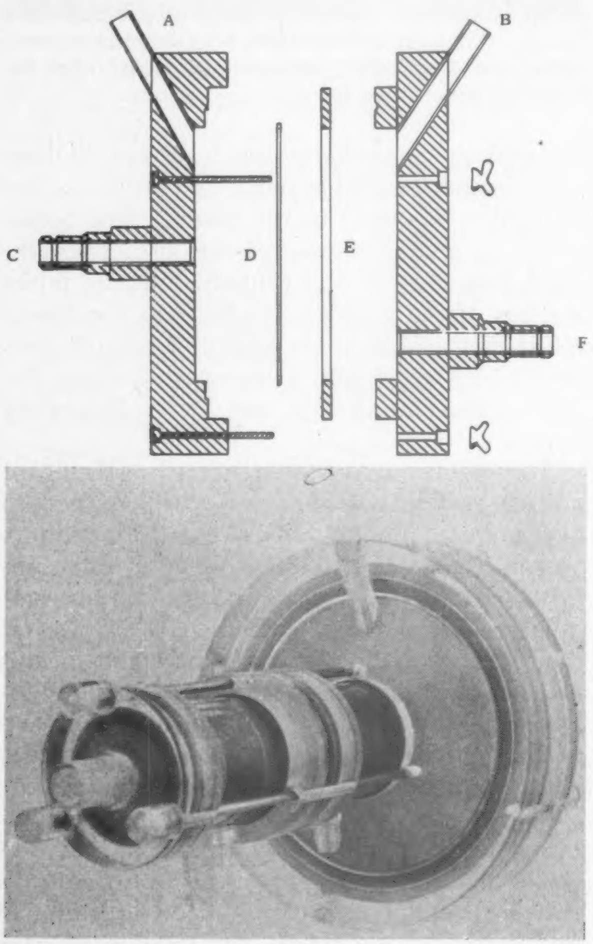


FIG. 3. Gemeinhardt bubble filter trap. *Top*, diagram of disassembled filter trap. *Bottom*, photograph of assembled filter trap. Upper tube endings are for the purpose of eliminating any entrapped air bubbles.

The filming oxygenators have evolved in two clinically different directions. In the fixed screen or Gibbon[9,10] types the venous blood is distributed in a thin film over a stainless steel screen similar in appearance to ordinary metallic window netting. The screens are displayed in "battery plate" order within an atmosphere of gaseous oxygen. Diffusion of oxygen and carbon dioxide takes place across the oxygen-blood interface of this film as in the bubble oxygenator.

In the revolving disc (Björk, Kay-Cross) type of filming oxygenator[25–27] the blood is spread by centrifugal force as a thin film over the surfaces of multiple discs revolving within an atmosphere of gaseous oxygen (Fig. 2). Dependently they dip into a trough containing venous blood. Again oxygenation takes place across the oxygen-blood interface provided by the film surface.

The filming oxygenators have a significant advantage over the bubble oxygenators in that bubbles are not formed. They have a disadvantage in that their oxygenating capacity is logistically restricted. They are slower in starting to function because of the necessity for establishment of the filming surface. Finally, just as in the bubble type, it is necessary in this oxygenator to expose the oxygen in "caustic" concentrations directly to the blood surface.

The diffusion or membrane types of oxygenator interpose a semipermeable membrane between the fluid blood and the gaseous oxygen. The Kolff[28,29] and the Clowes[30,31] oxygenators are representative of this group. While physiologically they approach the function of the natural lung more closely than do the other types of oxygenators, and may well be the prototype of that of the future, at present they offer so much difficulty both logistically and in practical application (leakage, irregularities of flow and difficulty in preparation) that they are seldom used clinically.

FILTRATION MECHANISM

The "bubble filter-trap" usually consists of a combination of a screen (metallic or plastic) which filters out gross particulate matter, such as fibrin clots, and a separation chamber which will entrap floating bubbles of gas[32–34] Authorities differ as to the relative advisability of place-

ment of such a trap before or after the left ventricular pump in the line of extracorporeal flow (Fig. 3).

CANNULATION

In open heart surgery for ventricular septal defects the venae cavae must be intubated individually (Fig. 4). Either plastic or stainless steel cannulas[3] may be used. They are inserted separately through purse-stringed stab wounds made in the right atrium or its appendage. The caliber should approximate one-half the cross-sectional area of the respective vena cava. Tapes are passed intrapericardially about each vena cava and are incorporated within segments of semirigid rubber tubing for reliably controllable constriction of these vessels.

The two cannulas are connected securely to the "venous" line of the extracorporeal circuit by a Y-connection of plastic material or stainless steel. When the bubble oxygenator is used no great effort need be made to exclude all air from the tubing at the time of connection since the oxygenator automatically will eliminate it. With other types of oxygenator more care must be taken, although the filter trap will suffice to prevent moderate amounts of entrapped air from entering the arterial circulation.

The arterial cannulation may be performed upon the subclavian artery, one or both of the femoral arteries, or the ascending aorta itself. The latter site of arterial cannulation is particularly advantageous in small children and in infants in whom the vessels to the extremities may be very small. When pulsatile flow pumps are used tubing and cannulas of somewhat larger size are required to avoid extreme fluctuations in pressure. Therefore, direct cannulation of the ascending aorta with a tube of large caliber is preferable when a pulsatile flow system is used (Fig. 4).

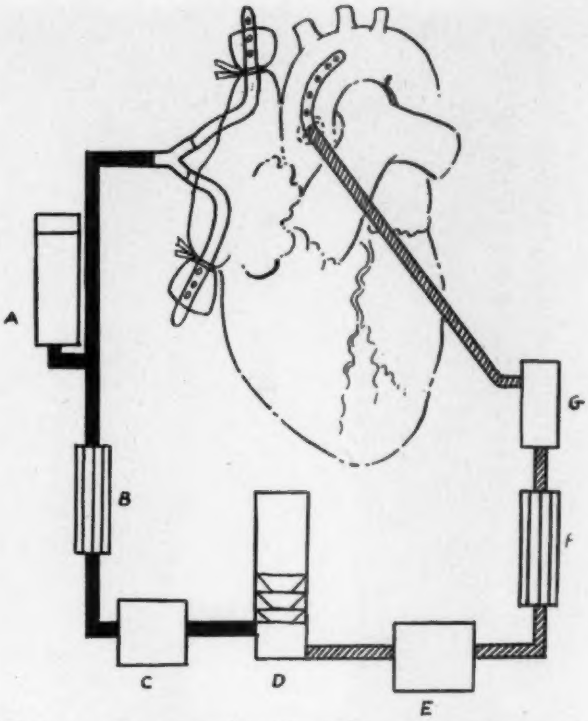


Fig. 4. Diagrammatic illustration of extracorporeal circuit used by us for repair of ventricular septal defects. Note individual cannulation of the venae cavae and of the ascending aorta. This latter cannulation is most advantageous in small infants and in all patients when a pulsatile flow pumping system is used. A, venous reservoir. B, Jehle or Ivan Brown heat exchanger. C, pump head which can be eliminated if gravity drainage is utilized to aspirate the bodily venous return. D, oxygenator. E, left ventricular pump. F, Jehle or Brown heat exchanger. G, bubble filter trap.

THE LOW PRESSURE ASPIRATOR

Constriction of the cannulated venae cavae by the encircling tapes serves to divert the entire systemic venous return into the extracorporeal circuit. However, there remain two significant sources of venous return to the heart: (1) the coronary sinus and Thebesian return of the myocardial circulation which is chiefly to the right atrium, and (2) that from the bronchial arteries to the left atrium by way of the pulmonary veins. Not only does this "auxilliary" blood return tend to flood and obscure the operative field, but also continued loss of this blood from the combined corporeal-extracorporeal circuit soon depletes the circulating volume seriously. This blood can be aspirated and returned to a reservoir suitably placed in the extracorporeal circuit by the use of a "low pressure" aspirating device. However, when both blood and air are aspirated either simultaneously or alternately, great turbulence and serious blood trauma may result. Therefore, the low pressure suction should be turned on only when sufficient blood has collected to permit complete immersion of the terminal apertures of the aspirator tip beneath the surface of the blood.

RATE OF EXTRACORPOREAL FLOW

While there still remain significant differences of opinion as to the optimal rate of bodily perfusion, it is generally believed that a flow rate of not less than 50 cc. per minute per kilogram of body weight is essential for maintenance of satisfactory organ and tissue vitality at normal body temperatures. Usually perfusion of an

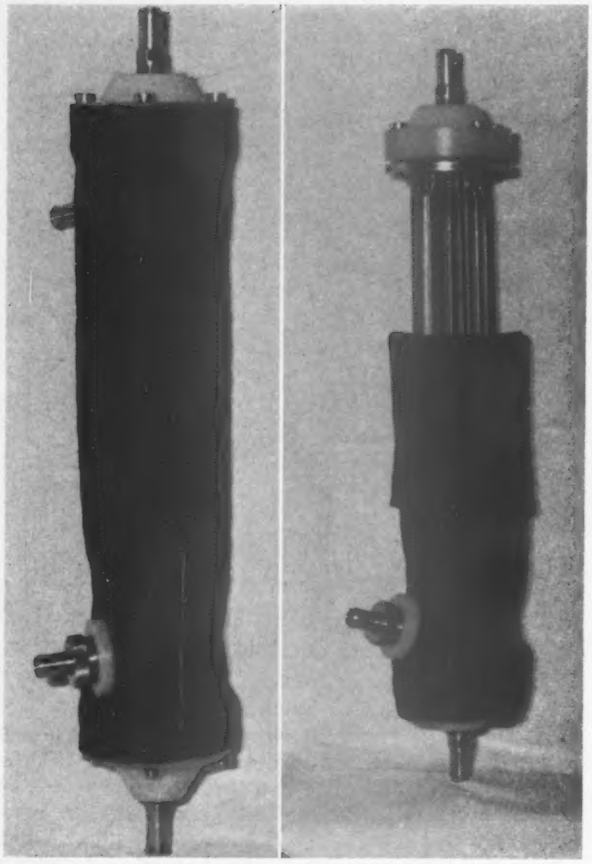


FIG. 5. Jehle heat exchanger (modified from Ivan Brown). *Left*, with rubber water jacket in functional position. *Right*, with rubber water jacket rolled down to expose flattened metal tubes for passage of blood.

amount equal to the systemic venous return will suffice, providing that this rate of flow maintains a mean arterial blood pressure of 65 mm. Hg or more. Should the arterial pressure (measured directly through polyvinyl tubing inserted into a systemic artery) fall below this level, transfusion into the system from the reservoir and/or an increase in the rate of perfusion will tend to elevate it. If these measures do not suffice, the judicious administration of one of the vasopressor agents may prove helpful.

COMBINATION OF CIRCULATORY BYPASS WITH HYPOTHERMIA

In certain clinics general body hypothermia is induced at the time the perfusion is established. Usually, a heat exchanger such as that devised by Brown and Sealy[35] will have been incorporated within the bypass circuit. Ideally two should be used, one on the "arterial" side for cooling, and one on the "venous" side for rewarming (Fig. 5). This technic allows for the greater affinity of hemoglobin for oxygen at lower temperatures and protects the patient against the possibility of air embolism from the sudden release of gaseous oxygen upon re-entry of cool blood into the warmer body.

The cooling of the patient so lessens his circulatory needs that the extracorporeal perfusion rate may be reduced appreciably. Not only does this reduce the logistical problems and tend to minimize trauma to the blood, but also momentary complete interruption of the circulation (by stopping the pumps) is permissible if desirable for technical reasons. Needless to say, the bypass must not be terminated finally until the body temperature has been raised to such a level that spontaneous continued rewarming may be counted upon. In adult patients rewarming of the entire body mass may necessitate considerable prolongation of the bypass time. In part this is due to the difference between the temperature gradient from normothermia (37°C.) to the uppermost permissible limit of blood warming (40°C.) and that from normothermia to the lowest limit of feasible blood cooling (5°C.). In part it may be attributed to the existence of a relatively huge mass of cold inert tissue (skin, subcutaneous fat and extremities) which tends to recool the central tissues as soon as the perfusion is interrupted. Following completion of the definitive procedure the operator may be reluctant to prolong the perfusion beyond a rather short period.

Rewarming by diathermic means at this stage has been found to be most advantageous.

ELECTIVE CARDIAC ARREST

Melrose,[36,37] Effler,[38] Lam,[39] Kirklin[40] and others have utilized cardioplegic drugs to bring about a cessation of ventricular contractions. Thus a quiet operative field is obtained which facilitates the reparative suturing. Unfortunately the ascending aorta must be cross-clamped during the period of cardiac arrest, thus interrupting coronary perfusion and bringing about a state of myocardial ischemia (and hypoxia). Recent research[41–48] has cast fundamental question upon the desirability of elective cardiac arrest in open heart surgery and the method is being used less often than formerly.

TERMINATION OF THE BYPASS

Considerable care should be taken to evacuate any entrapped air from the respective ventricles both at the time of final closure of the septal defect, and again at the time of the application of

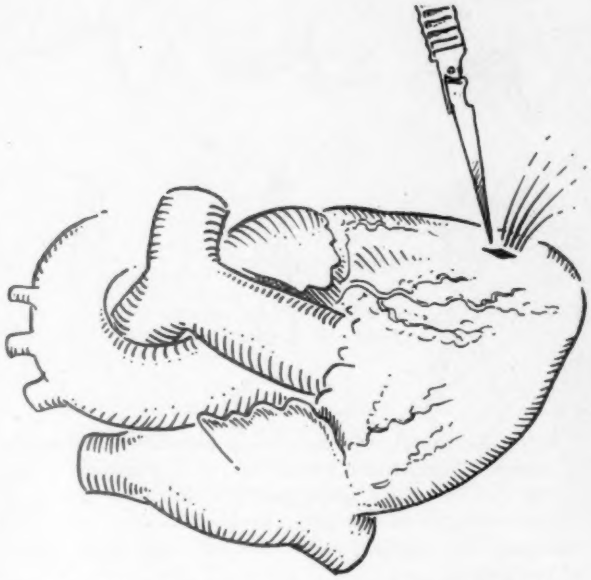


FIG. 6. Venting the left ventricle. An incision, 1 cm. long, into the contradependent portion of the left ventricular chamber will permit escape of any entrapped air (along with some blood).

FIG. 7. Radiogram of E. G., forty-nine year old white female patient with complete heart block (idiopathic), revealing the location of the special catheter electrode, the tip of which has been introduced by way of the right innominate vein into the right ventricle.

the last sutures to the incision in the right ventricle. If there is any doubt as to retention of any air bubbles, the apex of the heart should be elevated and kept so until the left ventricle can be vented adequately. This is best done by making a stab wound 1 cm. long near the apex. The lips of this incision are spread apart with fine curved hemostats and the contracting ventricle is permitted to expel any contained air as well as a small amount of blood (Fig. 6). Should the cardiac contractions be weak or incoordinate the ventricular air and blood content may be evacuated by rhythmic manual compression.

By the time the heart wall has been repaired the ventricles should be contracting vigorously, permitting the rate of mechanical pumping to be reduced (the vena caval tourniquets having been released). Gradually more and more of the circulatory load is returned to the heart until finally the pumps may be stopped completely. Should the cardiac action thereafter flag, the pumps may be restarted, and a more gradual "weaning" program carried out. Intravascular administration of calcium chloride or gluconate in doses up to 1 gm., digitalis in its quicker acting forms or dilute epinephrine solution as a drip, often prove helpful under these circumstances. Intravenous administration of potassium chloride will serve to "neutralize" any inadvertently administered excess of digitalis. Isoproterenol (Isuprel®) or atropine may be used if mechanical injury or metabolic depression of the conduction system has taken place. The vasopressive agents have limited value at this point.

BLOOD VOLUME

The question of hypo- or hypervolemia now arises. This problem presents itself in aggravated form in small children or infants. Hypovolemia may lead to immediate or delayed hypotension or shock. Hypervolemia may precipitate the onset of acute pulmonary edema. Sources of blood loss in these procedures are so many and often so considerable that ordinary measures of estimation of loss are almost useless. While the level of the venous pressure (monitored electronically) may provide a valuable clue, a significant change in the body weight (compared with an immediate preoperative determination) offers sounder guidance. Special weighing devices now are available for use on the operating table.[44]

CONDUCTION DEFECTS AND HEART BLOCK

Pre-existent conduction defects in congenital heart disease usually do not constitute an appreciable additional hazard to open heart surgery since the patient will have become fully adjusted to them.

While suturing into or about the ventricular

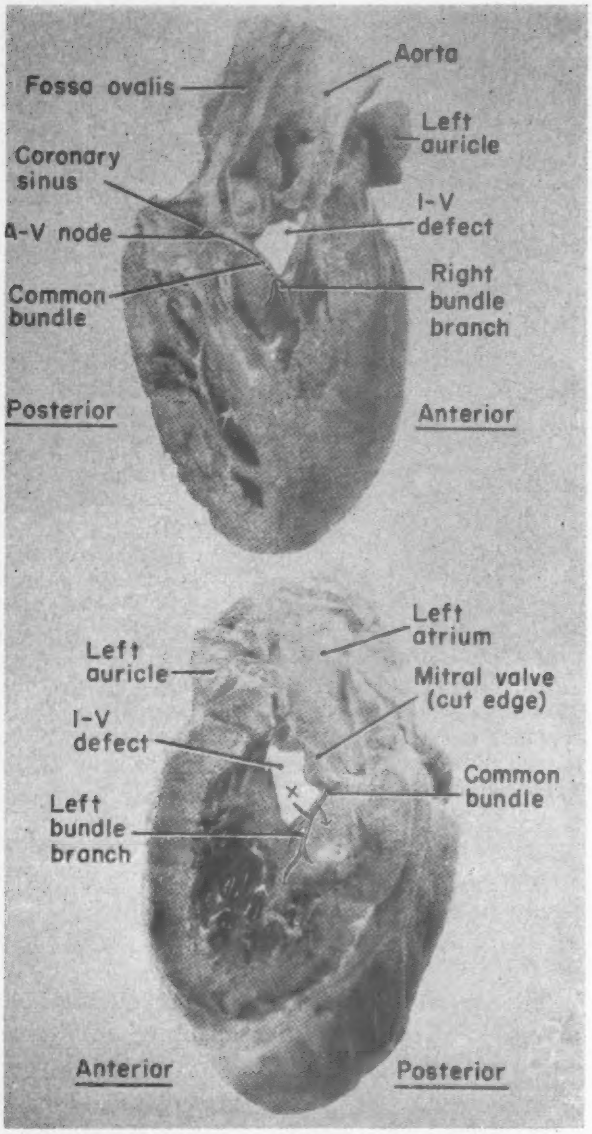


FIG. 8. Usual course of atrioventricular conduction bundle in patients with ventricular septal defect. (From: TRUEX, R. and BISHOP, J. K. *J. Thoracic Surg.*, 35: 432, 1958.) *Top*, right ventricular aspect. *Bottom*, left ventricular aspect.

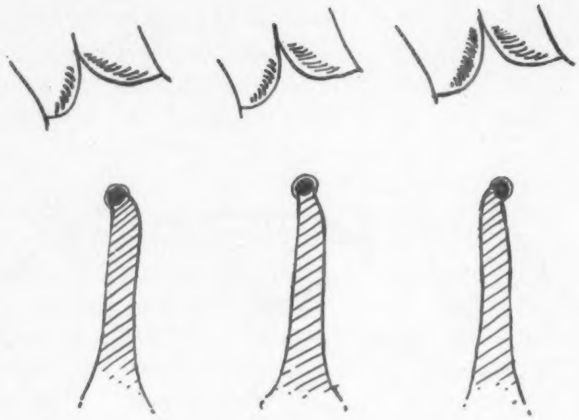


FIG. 9. Sectional view indicating possible relationships of common conduction bundle to the free margin of the septal defect in its dorsocaudal quadrant. A, usual course to right of margin. B, bundle runs on septal margin. C, bundle deviates to left ventricular aspect of margin.

septum one may interrupt either the main atrioventricular conduction bundle (His) or one of its major branches. Myocardial anoxia and certain metabolic disturbances also may produce various types of heart block. These latter lesions, fortunately, are transient in nature and usually resolve spontaneously, providing the effectiveness of the heart as a pump is maintained at an adequate level and blood chemistry is within normal limits. Ventricular stimulant drugs, such as epinephrine (in drip), isoproterenol or atropine, may be life-saving at this point. Sometimes direct ventricular stimulation by an electrical pacemaker will be necessary,[45] preferably by means of a wire inserted directly into the right ventricular myocardium or in the lumen of the outflow tract. These measures should be continued until the electrocardiogram reveals that normal conduction has returned.

Right bundle branch block is such a common finding after surgical closure of a ventricular septal defect that it is often considered an accompaniment rather than a complication of the procedure. Its benign clinical course often seems to justify this opinion. On the other hand, *left bundle branch block*, while rare after such operations, imposes a serious handicap upon the heart.

Complete heart block due to actual surgical division or suture encirclement of the main conduction bundle may be permanent and often threatens survival. The early fortuitous establishment of an independent (slow) ventricular rhythm does not necessarily imply the restoration of an adequate cardiac output. Treatment consists of the administration of the previously mentioned medications (epinephrine, isoproterenol or atropine) and the use of an electrical pacemaker in the hope that atrioventricular conduction will return or that an effective independent ventricular rhythm will become established. Isoproterenol is the drug of choice and the first dose should be administered prior to closure of the chest.

ELECTRICAL PACEMAKERS

When the existence of complete heart block is recognized at the operating table, an insulated

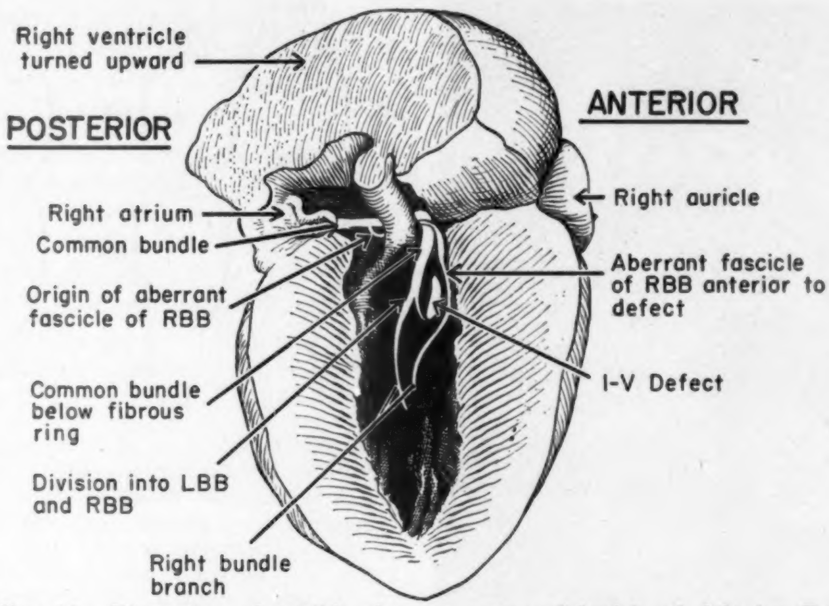


FIG. 10. Illustration of possible aberrant course of fascicle of right bundle branch which may be injured easily during repair of a ventricular septal defect. (From: TRUEX, R. and BISHOP, J. K. *J. Thoracic Surg*, 35: 428, 1958.)

metallic wire should be placed so that its free end is buried within the thickness of the myocardial wall in the outflow tract area close to the septum. The wire is then brought out upon the skin surface through an independent puncture wound. An "indifferent" (wire) electrode is attached to the skin and subcutaneous tissues of the chest wall in the region of the precordium. Thereafter, by rhythmic application of electrical pulses of appropriate curve, frequency and intensity, the rate of cardiac contraction can be regulated at the desired level. Unfortunately, in time the wire endings stimulate a fibrosing reaction within the myocardial tissue so that they tend to become "walled-off" and less directly in electrical contact with the heart. For this reason the electrode tip should be positioned preferably in the lumen of the right ventricular outflow tract. Such a catheter electrode may be inserted via the right transverse cervical vein. While the cardiac mechanism may become so adjusted after an interval that it thereafter can maintain an adequate circulatory output with or without the aid of isoproterenol, there is no guarantee of this.

Recent interesting experiences with the use of catheter electrodes which can be inserted within the cardiac chambers and the development of readily portable battery-powered pacemakers[45] offer considerable hope for better methods of permanently pacing the heart with complete atrioventricular block (Fig. 7).

PREVENTION OF HEART BLOCK

The anatomical demonstrations of the usual course of the atrioventricular conduction system in human hearts with ventricular septal defects by Truex and Bishop[46] have shed much light upon the surgical creation of heart block. Kirklin et al.[47] and others[48,49] have pointed out danger points in the placement of sutures into the ventricular septum. It appears that the main atrioventricular conduction bundle after piercing the fibrous "ring" of the tricuspid valve runs subendocardially upon the right side of the ventricular septum. When a ventricular septal defect exists, the bundle usually runs around its margin in the dorsocaudal quadrant (Fig. 8). While it usually lies upon the right ventricular aspect of the septum close to the free edge, particularly in the case of larger defects, it may "move over" to run along the center of the edge or even to the left ventricular aspect of the edge (Fig. 9). In the latter instance it would seem that the bundle necessarily would be encircled by any type of suturing except a "tangential" one such as that which has been described[48] for the purpose of avoiding it.

However, as Truex[46,50] has pointed out, there may be a number of variations in the course of the main conduction bundle which sometimes may split in two, one portion passing upward along the upper (cephalodorsal) margin of the defect while the other follows its more usual lower (dorsocaudal) course (Fig. 10). Allen,

FIG. 11. Photograph taken at operation which demonstrates the large size of the pulmonary artery and the rather underdeveloped aorta which is seen commonly in patients with ventricular septal defect. (1) Superior vena cava. (2) Right auricular appendage. (3) Hypotrophic ascending aorta. (4) Large dilated pulmonary artery. (5) Right ventricular outflow tract. View from the right side.

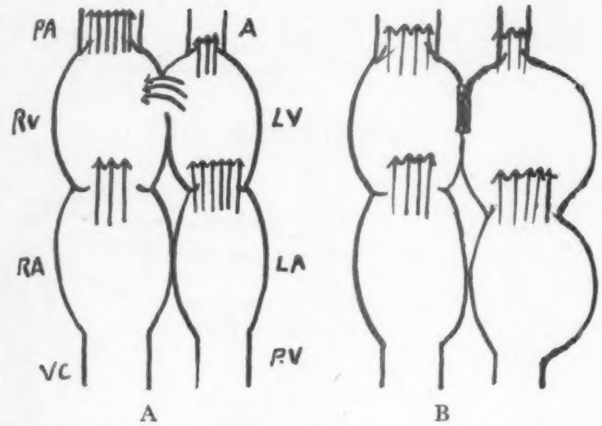


FIG. 12 Diagrams to illustrate congestion of the left ventricle and left atrium which may develop when a large left-to-right shunt suddenly is interrupted by closure of a ventricular septal defect. While minimal bodily requirements are unchanged after the surgery, there is no reserve or safety factor for the left ventricle. A, preoperative status. B, postoperative status. If the blood volume is increased even slightly by overtransfusion, the left ventricle may decompensate, causing acute (hemorrhagic) pulmonary edema.

Lederman and Pearl[51] have been able to demonstrate the conduction system visually by painting the septum with an aqueous solution of 5 per cent iodine dissolved in 10 per cent sodium iodide at the time of operation. Such exact knowledge of the course of this most important structure should permit the placement of sutures with critical accuracy and may serve to obviate further accidents of this type.

Prevention of Sudden Severe Intracardiac Pressure Changes

When a ventricular defect is closed completely by mechanical (surgical) means two things happen immediately: (1) the dynamic competition between the ventricles is broken and (2) the shunt (if any) through the defect is interrupted. These would seem to be most salutary developments, and obviously should be if the heart and lungs were otherwise entirely normal. In the person with a small septal defect through which occurs but a small left-to-right shunt, with normal pulmonary arterial pressures and with no pulmonary vascular deterioration, these conditions are approached. In such persons brilliant surgical results are obtained, the few operative fatalities being related generally to technical errors, to blood incompatibility or to mechanical malfunction of the extracorporeal equipment.

Defects with Large Left-to-Right Shunts

Unfortunately, the presence of a large (but otherwise uncomplicated) ventricular septal defect characteristically is associated at least initially with a large left-to-right shunt. Unless a significant increase in the pulmonary vascular resistance has developed, the left ventricle will have become accustomed to use the right ventricle and the pulmonary vascular bed as an additional or an auxilliary outflow tract. This is facilitated by the marked increase in the size of the pulmonary artery (and its ramifications) which is characteristic of these cases (Fig. 11). Moreover, since the pulmonary vascular resistance is much lower than the systemic (characteristically in these cases it is higher than normal, being expressed by definite elevation of the pulmonary arterial pressure), a large portion of the left ventricular blood content is diverted from the aorta. As a result, this vessel may be small and relatively underdeveloped. Complete closure of the ventricular septal defect cannot be accomplished suddenly in this type of case without serious consequences. The relatively hypotrophic aorta (and its ramifications) will not be able readily to accommodate itself to the abrupt increase in volume flow. The left intraventricular pressure (especially the end

diastolic level) may rise and the chamber become visibly dilated (Fig. 12). The left atrial pressure will rise at times to 70 to 80 cm. of water. This increased pressure, which is transmitted directly via the valveless pulmonary veins to the capillaries of the lungs, is capable of precipitating acute pulmonary edema, an observation first made by Kolff and his associates.[52] This tendency can be exaggerated by the excessive administration of fluid or blood, and apparently also is aggravated by the loss of myocardial tone which accompanies the induction of elective cardiac arrest (or the hypoxia associated therewith).

Measures to Prevent Left Atrial and Ventricular Dilatation: Kolff et al.[52] advise definitive (temporary) drainage of the left atrium with a catheter for a time after termination of the bypass in order to reduce the incidence of this complication. Sirak and Hosier[53] urge the creation of a communication between the pulmonary artery and the aorta (an artificial patent ductus arteriosus) at the time of closure of a ventricular septal defect. At a second operative stage they propose that the new communication be obliterated.

It has seemed to us that while merit is inherent in these two different suggestions, a simpler and surer way to handle this situation is to create a small defect in the muscular portion of the atrial septum. Such a defect will provide prolonged decompression of the left atrium, thus permitting gradual adjustment of the left ventricle and the systemic arteries to the altered hemodynamic situation. The experimental work of Swan et al.[54] and Blanco[55] clearly indicates that such artificially created atrial septal defects, unless made larger than 1.5 cm. in diameter, invariably will close off spontaneously. The experience in our clinic with over 100 such defects created deliberately during the course of surgery for mitral stenosis[56] has confirmed this overwhelming tendency toward spontaneous obliteration (usually within a period of eight weeks).

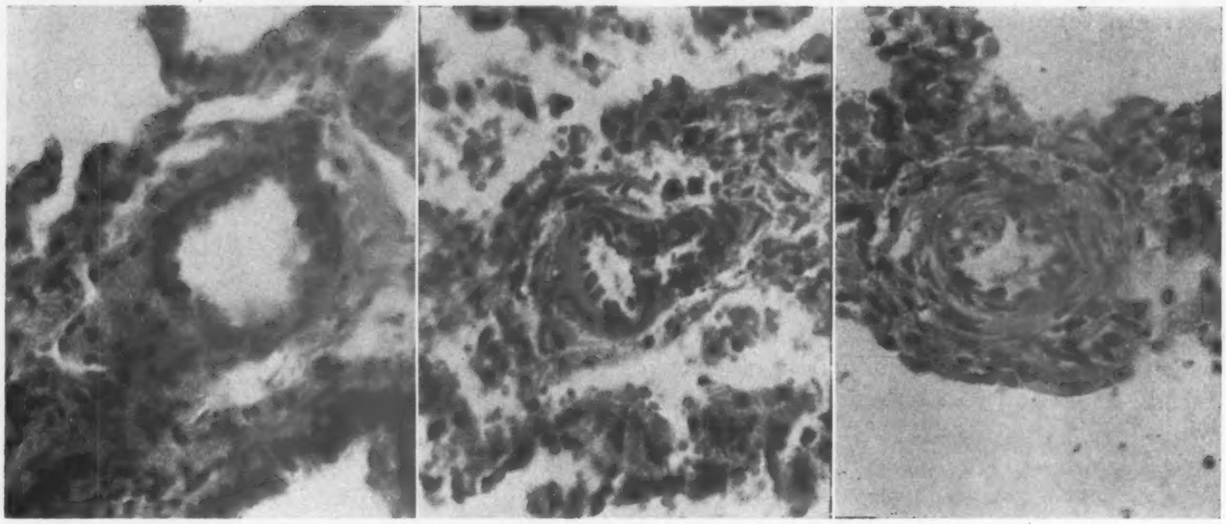
Therefore, it is now our routine policy, in patients with a large ventricular septal defect and a large left-to-right shunt, *electively to create such an atrial septal defect* through a right atrial incision after opening the right ventricle but before closing the ventricular septal defect. The atrial defect is made roughly in proportion to the size of the heart (0.4 to 1 cm. in diameter and is placed in the dorsal (muscular) portion of the septum, well away from the fossa ovalis and

Fig. 13. Drawing of interior of right atrium showing method of creating a transient atrial septal defect to provide a "safety-valve" in case of overloading of the left side of the heart.

the ostium of the coronary sinus (Fig. 13). The external atrial wall is repaired with two rows of sutures and then the ventricular septal defect is attacked in the customary manner. In most of these cases the size of the defect will require that it be closed with the aid of prosthetic material (in our clinic a patch of compressed Ivalon® sponge reinforced with Teflon® mesh for permanence and strength is used).

DEFECTS ASSOCIATED WITH PULMONARY HYPERTENSION

When a large ventricular septal defect has existed for a considerable (but extremely variable) period of time, the pulmonary arteriolar and the total pulmonary vascular resistances gradually become higher until they become first equal to, and eventually greater than the corresponding values for the aortic system. This is accompanied by progressive elevation of the pulmonary arterial pressure until it equals that within the aorta. The persistence of such pulmonary hypertension is associated with the progressive development of pulmonary arteriolosclerosis. The changes in the pulmonary arterioles take the form of intimal thickening and hyperplasia, medial proliferation and adventitial fibrosis (Fig. 14). The net result of these changes is a great thickening of the vessel wall at the expense of the lumen. Ultimately, fibrous obliteration with or without true luminal thrombosis takes place. The original large left-to-right shunt in such cases becomes progressively reduced with the increase of the pulmonary vascular resistance, first to a smaller one, then a negligible one, then to a biphasic or "equalized one" (in which there is both left-to-



A B C

FIG. 14. Pathological changes in the pulmonary arterioles due to a ventricular septal defect with a left-to-right shunt. Original magnification × 80. Courtesy J. Imbriglia (unpublished work). A, Early vascular changes consisting chiefly of medial thickening. B, Moderately advanced changes in which intimal hyperplasia is beginning. C, Advanced pulmonary arteriolar degeneration and great increase in the thickness of the vessel wall at the expense of the lumen. At this stage, severe pulmonary hypertension will be present almost invariably.

right and right-to-left shunting of minor degree) until finally it is replaced by a predominantly right-to-left shunt. In the latter instance arterial oxygen unsaturation and finally frank clinical cyanosis will become evident.

Obviously the end-stage of this condition is a hopeless one. Presumably, however, resolution of many of the earlier changes is possible and indeed even probable, if the initiating factors—volume overload and hypertension of the pulmonary arteriolar bed—can be eliminated. Hence, every effort should be made to close the defect in such cases before the "point of no return" has been reached. Once clinical cyanosis (due to a large right-to-left shunt through the defect) has appeared, it generally is believed that the condition has become hopeless.

Because of the progressive reduction, elimination or beginning reversal of this shunt, the originally small aorta may become enlarged or otherwise so adjusted that it is readily capable of accepting the entire left ventricular output. Indeed it even may come to act as an auxiliary or additional outflow tract for the otherwise significantly obstructed right ventricle. Therefore, the surgical problems are quite different in these patients from those encountered in earlier cases. Not the reserve of the left ventricle but that of the "obstructed" right ventricle may be compromised by the sudden closure of the defect. This tendency may be exaggerated and acute right ventricular decompensation may occur during the operative or postoperative period by the development of pulmonary atelectasis or pneumonitis which will seriously reduce the effective size of the pulmonary vascular bed, by the excessive administration of blood or fluids, or, perhaps, by the development of "spasm" of the pulmonary arterioles.

Measures to Prevent Right Ventricular Failure Following Closure of Defect: In such a case the maintenance of a "safety-valve" by which a portion of the systemic venous return might bypass the partially obstructed right heart might well prove life-saving. Since all the precipitating factors mentioned are transient in their effect it would seem sufficient if the safety-valve mechanism likewise were but a temporary one, the effect of which would be lost relatively soon after the patient had recovered from the operative procedure.

The creation of such a safety-valve necessarily would entail the production of a communication at a suitable point between the greater and lesser circulatory systems. The creation of an aorticopulmonary arterial communication as proposed by Sirak and Hosier[53] has not met with significant clinical acceptance. A communication at the ventricular level is extant at the time of operation in these cases. Partial closure by mere reduction in the size of the defect obviously is unacceptable. Presumably it might eventuate in some slowing of the process of deterioration, but it certainly could not lead to cure unless

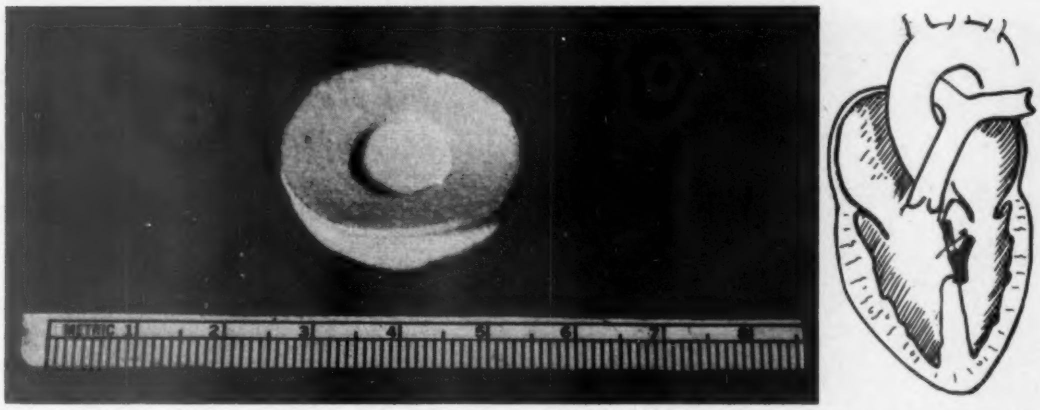


FIG. 15. The prosthetic foraminal valve. *Left,* actual prosthetic prepared for correction of a large septal defect. *Right,* method of placement of the artificial (prosthetic) foraminal valve in a ventricular septal defect to permit temporary continuation of a right-to-left shunt. This technic is used by us in the one-stage correction of tetralogy of Fallot.

it were planned as part of a two-stage program. The suggestions of Lewis et al.[57] and Lillehei[58] that gradual closure of a ventricular septal defect might be accomplished by utilization of a "leaky" patch of plastic sponge do not seem to be feasible with our available prosthetic materials and technics. If the residual communication is small it tends within a few hours to become blocked by formation of a fibrin clot, thus rapidly completing the closure. A somewhat larger residual communication probably would not close at all thus perpetuating the communication. Cooley's[59] two clinical experiences with late physical rupture of plastic (Ivalon) patches used for closure of ventricular septal defects with subsequent (proved) restoration of the shunt would seem amply to confirm this theoretical objection.

At our clinic[60] a two-leaved valvular prosthesis of Teflon reinforced Ivalon (formalinized polyvinyl) sponge was devised to maintain for a time a portion of the original right-to-left shunt in patients with the tetralogy of Fallot (Fig. 15). This "artificial foraminal valve," sutured to the margins of a ventricular septal defect, becomes closed functionally whenever the pressure within the left ventricle exceeds that within the right ventricle but opens partially to equalize their respective tensions whenever the converse is true. With the passage of time, the interstices of the sponge become impregnated with fibroblasts and connective tissue fibers, and the "leaves" of the prosthesis gradually become fused together, completely interrupting the communication. The process of physical closure may take as long as three months, but (as in the natural foramen ovale) functional closure will be established at once if there should prove to be no physiological need for it. In other words, if the level of the pulmonary vascular resistance is such that the level of pulmonary arterial (and right intraventricular) pressure falls below that of the left ventricle, functional closure of the prosthesis will be immediate. Nevertheless, the safety-valve mechanism will remain effective for several weeks, thus enabling the circulatory apparatus to make the necessary adjustments in the event that some unforeseen development (such as a possible postoperative pulmonary complication) should suddenly increase the pulmonary vascular resistance.

Whether such an "artificial foraminal valve" has a worthwhile place in the treatment of a patient with a ventricular septal defect and pulmonary hypertension and pulmonary vascular change remains to be seen. While this technic has been used in a number of patients operated on at our clinic, in the majority of patients with a ventricular septal defect closed by suturing or patching, a small (5 to 10 mm.) defect has been created electively in the dorsal (muscular) part of the atrial septum. A most satisfactory outcome has been the usual result. Apparently a right-to-left shunt will occur through such a defect when it is physiologically necessary as readily as a left-to-right one under converse conditions.

Selection of Time, Procedure and Patient for Surgery

Not only must the proper patient be selected for surgery but also the proper type and time of surgery must be selected for the individual patient. The various pertinent principles and

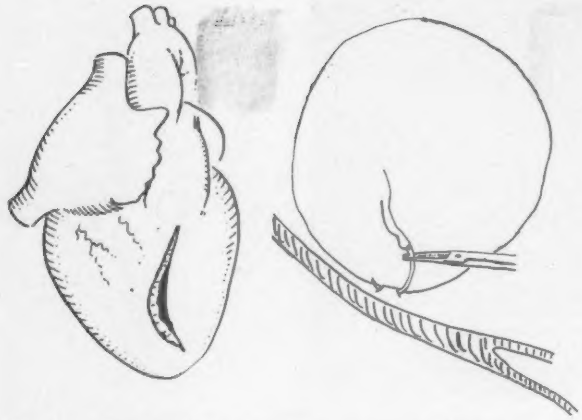


FIG. 16. Technic for repair of a ventricular septal defect. *Left*, long incision made through the "avascular" area of the right ventricular wall. They may be curved or angulated to evade all large coronary arterial branches. *Right*, method of "tangential" placement of sutures into and along the margin of the dorsocaudal quadrant of the defect.

the special criteria for making such decisions have been broached during the preceding discussion and in previous papers of this Symposium but, for the sake of clarity, an effort will be made to epitomize them now as best we can.

(*1*) *Early Infancy:* Since tiny infants tolerate definitive corrective surgery poorly, we believe that an attempt should be made to "carry them along" by medical means until they are old enough and strong enough to undergo the necessary definitive procedures. Preferably, they should be two years of age or slightly older, certainly more than one year old if this is at all feasible. However, if there is strong reason to doubt that the patient will survive the first twelve months of life, a "banding" operation[61] should be carried out to narrow the pulmonary artery and to abolish much or all of the left-to-right shunt. At a later stage (three years) the patient should undergo surgery again for definitive closure of the defect.

(2) *Uncomplicated Defects:* In patients between two and fifty years of age with small ventricular septal defects, with predominant left-to-right shunts and with pulmonary arterial pressures less than two-thirds of the systemic levels, a corrective operation is urged at once unless there is a contraindication. The operative risk is so small, and the surgical results obtained in such cases in properly organized clinics are so satisfactory, that little consideration should be given to temporizing policies. If the operation is not carried out at this favorable time, the majority of such patients will eventually come to fatality essentially because of the persistence of the defect and the resulting shunt. There is little to be gained by waiting to be sure that the patient cannot survive without surgery; by then the patient will either be lost or will return as a less favorable or even as a desperate risk. The elective creation of an interatrial septal defect at the time of operation will prevent possible left ventricular failure and acute pulmonary edema. However, if the ventricular septal defect is small, this may be unnecessary.

(3) *Pulmonary Hypertension without Right-to-left Shunt:* Patients with definite pulmonary hypertension (two-thirds or more of systemic pressure levels) but without a predominant right-to-left shunt should be operated on. Again, an interatrial septal defect should be created just before closing the ventricular septal defect, thus reducing the likelihood of postoperative right ventricular failure. While the operative risk in this type of case is somewhat larger than in the more favorable cases, it can be kept at an acceptable level (about 10 per cent) by careful observance of all the various recognized details of present day surgical and medical management. In most cases sufficient reversal of the already established pulmonary vascular changes will take place to provide an excellent long term clinical result.

(4) *Pulmonary Hypertension with Reversal of Shunt:* It is our present feeling that patients with pulmonary vascular change sufficiently severe to cause a preponderant right-to-left shunt are hopelessly advanced and do not represent reasonable operative risks.

(5) *Other Contraindications for Surgery:* In any given patient there may be pertinent practical considerations which will militate against or even contraindicate surgical intervention, e.g., feebleness, advanced age, coexisting systemic disease of other organ systems, coexisting congenital or acquired heart disease. Any or all of these may be sufficient.

OPERATIVE TECHNIC

The bypass is started gradually until the entire cardiac output has been taken over by the pump. If hypothermia is to be induced, the heat exchanger in the arterial line is used until the temperature has been reduced to the desired level. Then the vena caval tourniquets are tightened, diverting all of the venous return into the extracorporeal circuit except that from the coronary circulation (coronary sinus and Thebesian veins) and that from the bronchial cir-

culation (by way of the pulmonary veins). The anterior wall of the right ventricle is sectioned longitudinally through its "avascular" area (Fig. 16). Its blood content is evacuated by the low pressure suction device and this is utilized as necessary throughout the procedure. This blood is returned to a reservoir in the extracorporeal circuit. The lips of the ventricular incision are retracted and the septal defect is identified. If it is small (up to 6 to 8 mm. in diameter), it may be closed by simple suturing. In the dorsocaudal quadrant of the margin the sutures are placed in tangential fashion, as described (Fig. 16).

If the defect is appreciably larger a patch of prosthetic material may be required for repair without tension (Fig. 17). While compressed Ivalon sponge, Dacron fabric, Teflon mesh and many other substances may be employed, we have preferred a prosthetic "sandwich" consisting of two layers of Ivalon sponge compressed 6:1 with an intervening sheet of Teflon net mesh. The patch is cut to a suitable size and shape, being made somewhat smaller than the defect, and is sutured securely to its margins. Again, in the dorsocaudal quadrant a tangential type of suturing is employed. Interrupted simple or mattress sutures may be used for the remainder of the circumference of the defect.

After opening the right ventricular cavity, but before closing the ventricular defect, an incision is made in the right atrial wall and the atrial septum is exposed. Under direct vision, a 5 to 10 mm. linear incision is made through the dorsal portion of the septum, thus making a communication between the two atria. Care is taken to keep well away from the fossa ovalis and the ostium of the coronary sinus (Fig. 13).

The right atrial wall is repaired with two layers of sutures, one a continuous mattress type and one a simple running suture.

After obliteration of the ventricular septal defect, the ventricular wall is closed in similar manner. An attempt is made to evacuate all air from the right ventricle before placement and tying of the last few stitches. The left ventricle is vented thoroughly to expel any air which might be entrapped within it (or in the left atrium). The vent, too, is repaired with sutures.

The vena caval tourniquets are released and the body is rewarmed (if previously cooled) by using the heat exchanger in the venous line. When a satisfactory temperature level has been restored (measured in the esophagus or the pericardium) the bypass is slowed and finally terminated as the heart manifests its ability to resume the entire circulatory load.

FIG. 17. Autopsy specimen (left ventricular aspect) from a patient with severe pulmonary hypertension in whom the defect was sufficiently large to require closure with an Ivalon-Teflon prosthetic patch. Note close relationship of defect to aortic valve cusps suggesting the possibility of inadvertent injury.

SUMMARY AND CONCLUSIONS

Much progress has been made in the selection and surgical management of patients with ventricular septal defects. The technic of operative repair has been developed to a high state of perfection. Unhappily, secondary pulmonary vascular and myocardial changes essentially due to the effect of the long continued shunting of blood may sometimes render the outlook for these patients entirely hopeless whether treated medically or surgically. It is hoped in the future that these late developments and difficulties may be obviated by earlier recognition of the condition and operative correction at a more opportune time.

REFERENCES

1. LILLEHEI, C. W., COHEN, M., WARDEN, H. E., READ, R. C., AUST, J. B., DEWALL, R. A. and VARCO, R. L. Direct vision intracardiac surgical correction of the tetralogy of Fallot, pentalogy of Fallot, and pulmonary atresia defects: a report of the first ten cases. *Ann. Surg.*, 142: 418, 1955.
2. BAILEY, C. P., LACY, M. H., NEPTUNE, W. B., WELLER, R., ARVANITIS, C. S. and KARASIC, J. Correction of interventricular septal defects. *Ann. Surg.*, 136: 919, 1952.
3. SHUMACHER, H. B., JR. Experimental and clinical observations on the closure of cardiac septal defects. *Angiology*, 5: 289, 1954.
4. KAY, E. B. and ZIMMERMAN, H. A. Surgical repair of interventricular septal defects. *J. A. M. A.*, 154: 986, 1954.
5 BAILEY, C. P., DOWNING, D. F., GECKELER, G. D. LIKOFF, W., GOLDBERG, H., SCOTT J. C., JAN-

TON, O. and REDONDO-RAMIREZ, H. P. Congenital interatrial communications: clinical and surgical considerations with a description of a new surgical technique: atrio-septo-pexy. *Ann. Int. Med.*, 37: 888, 1952.
6. DOWNING, D. F., COOKSON, B. A., KEOWN, K. K. and BAILEY, C. P. Hypothermia in cardiac surgery. *J. Pediat.*, 44: 134, 1954.
7. GROW, J. B., DEMONG, C. V., and HAWES, C. R. Surgical treatment of ventricular septal defects: a method utilizing selective coronary perfusion and hypothermia. *J. Thoracic Surg.*, 32: 669, 1956.
8. PEIRCE, E. C., II, DABS, C. H and RAWSON, F. L. Isolated rupture of the ventricular septum due to nonpenetrating trauma: report of a case treated by open cardiotomy under simple hypothermia. *Arch. Surg.*, 77: 87, 1958.
9. KIRKLIN, J. W., DONALD, D. E., HARSHBERGER, H. G., HETZEL, P. S., PATRICK, R. T., SWAN, H. J. C., and WOOD, E. H. Studies in extracorporeal circulation. I. Applicability of Gibbon type pump oxygenator to human intracardiac surgery: 40 cases. *Ann. Surg.*, 144: 2, 1956.
10. GIBBON, J. H., JR. Application of a mechanical heart and lung apparatus to cardiac surgery. *Minnesota Med.*, 37: 171, 1954.
11. COOLEY, D. A., COLLINS, H. A., GIACOBINE, J. W., MORRIS, G. C., JR., SOLTERO-HARRINGTON, L. R. and HARBERG, F. J. The pump oxygenator in cardiovascular surgery: observations based upon 450 cases. *Am. Surg.*, 24: 870, 1958.
12. SWAN, H., VIRTUE, R. W., BLOUNT, S. G., JR. and KIRCHER, L. T., JR. Hypothermia in surgery: analysis of 100 clinical cases. *Ann. Surg.*, 142: 382, 1955.
13. BAILEY, C. P., MUSSER, B. G. and MORSE, D. P. The accomplishments of open heart surgery. *Am. J. Cardiol.*, 4: 147, 1959.
14. BAILEY, C. P. Surgery of the Heart. Philadelphia, 1955. Lea & Febiger.
15. KEOWN, K. K. Anesthesia for Surgery of the Heart. Springfield, Ill., 1956. Charles C Thomas.
16. GOLLAM, F. Physiology of Cardiac Surgery. Springfield, Ill., 1959. Charles C Thomas.
17. ALLEN, J. S. (Editor). Extracorporeal Circulation. Springfield, Ill., 1958. Charles C Thomas.
18. DEBAKEY, M. E. Simple continuous-flow blood transfusion instrument. *New Orleans M. & S. J.*, 87: 386, 1934.
19. GROSS, R. E. In: Allen, J. G. Extracorporeal Circulation, p. 25. Springfield, Ill., 1958. Charles C Thomas.
20. LILLEHEI, C. W., COHEN, M., WARDEN, H. E. and VARCO, R. L. The direct vision intracardiac correction of congenital anomalies by controlled cross circulation. *Surgery*, 386: 11, 1955.
21. MELROSE, D. In: Allen, J. G. Extracorporeal Circulation, p. 18. Springfield, Ill., 1958. Charles C Thomas.
22. MERENDINO, K. A., QUINTON, W. E., THOMAS, G. I., JOSEPH, J. E., HERROW, P. W., TREMBLAY, R. E., MAQUIRE, R. X. and VETTO, R. R. Description of a modified bubble-type pump oxygenator. *Surgery*, 42: 996, 1957.
23. PANICO, F. C. and NEPTUNE, W. B. A mechanism to eliminate the donor blood prime from the pump oxygenator. Presented at the 45th Clinical Congress of the American College of Surgeons, September 28, 1959, Atlantic City, N. J.
24. HARKEN, D. E. In: Allen, J. G. Extracorporeal Circulation, p. 29. Springfield, Ill., 1958. Charles C Thomas.
25. BJÖRK, V. O. Brain perfusions in dogs with artificially oxygenated blood. *Acta chir. scandinav.* (supp. 137), 96: 1, 1948.
26. CROSS, E. S., BERNE, R. M., HIROSE, T., JONES, R. D. and KAY, E. B. Evaluation of a rotating disc type reservoir oxygenator. *Proc. Soc. Exper. Biol. & Med.*, 93: 210, 1956.
27. DENNIS, C., SPRENG, D. S., JR., NELSON, G. E., KARLSON, K. E., NELSON, R. M., THOMAS, J. V., EDER, W. P. and VARCO, R. L. Development of a pump oxygenator to replace the heart and lungs: an apparatus applicable to human patients; an application to one case. *Ann. Surg.*, 134: 709, 1951.
28. KOLFF, W. J. and BALZER, R. R. Artificial coil lung. *Tr. Am. Soc. Art. Int. Organs*, 1: 39, 1955.
29. KOLFF, W. J., EFFLER, D. B., GROVES, L. K., PEEREBOOM, G. and MORACA, P. P. Disposable membrane oxygenator (heart lung machine) and its use in experimental surgery. *Cleveland Clin. Quart.*, 23: 69, 1956.
30. CLOWES, G. H. A., JR., HOPKINS, A. L. and KOLOBOW, T. Oxygen diffusion through plastic films. *Tr. Am. Soc. Int. Organs*, 1: 23, 1955.
31. CLOWES, G. H. A., JR., HOPKINS, A. L. and NEVILLE, W. E. An artificial lung dependent upon diffusion of oxygen and carbon dioxide through plastic membranes. *J. Thoracic Surg.*, 32: 630, 1956.
32. GILMAN, R. A., RUSSELL, R. L., MUSSER, B. G. and GEMEINHARDT, W. An air trap filter for extracorporeal oxygenator systems. *Surgery*, 42: 993, 1957.
33. MILLER, B. J., GIBBON, J. H., JR. and Gibbon, M. H. Recent advances in development of mechanical heart and lung apparatus. *Ann. Surg.*, 134: 694, 1951.
34. MILNES, R. F., VANDER WOUDE, R., MORRIS, J. S. and SLOAN, H. Problems related to a bubble oxygenator system. *Surgery*, 42: 986, 1957.
35. SEALY, W. C., BROWN, I. W., JR. and YOUNG, W. G., JR. A report on the use of both extracorporeal circulation and hypothermia for open heart surgery. *Ann. Surg.*, 147: 803, 1958.
36. MELROSE, D. G., DREYER, B., BENTALL, H. H. and BAKER, J. B. E. Elective cardiac arrest. *Lancet*, 269: 21, 1955.
37. BAKER, J. B., BENTALL, H. H., DREYER, B. and MELROSE, D. S. Arrest of isolated heart with potassium citrate. 273: 555, 1957.
38. EFFLER, D. B., GROVES, L. K., SONES, F. M., JR. and KOLFF, W. J. Elective cardiac arrest in open heart surgery: report of three cases. *Cleveland Clin. Quart.*, 23: 105, 1956.
39. LAM, C. R., GAHAN, T., SERGEANT, C. and GREEN, E. Experiences in the use of cardioplegia (induced cardiac arrest) in the repair of interventricular septal defects. *J. Thoracic Surg.*, 34: 509, 1957.

40. Kirklin, J. W. and McGoon, D. C. Surgical technique for repair of high ventricular septal defects. *J. Thoracic Surg.*, 35: 584, 1958.
41. Helmsworth, J. A., Kaplan, S., Clark, L. C., Jr., McAdams, A. J., Matthews, E. C. and Edwards, F. K. Myocardial injury associated with asystole induced with potassium citrate. *Ann. Surg.*, 149: 200, 1959.
42. Allen, P. and Lillehei, W. C. Use of induced cardiac asystole for open heart surgery; results in 70 patients. *Minnesota Med.*, 40: 672–676, 1957.
43. Bing, R. J. The metabolism of the heart. In: Harvey Lecture. Senis L. 27–1956. New York, 1956. Academic Press, Inc.
44. Paquin, A. J., Marshall, V. F., and Nathanson, B. Studies on a potential method for determination of operative blood loss. *Ann. Surg.*, 141: 53, 1955.
45. Bellet, S., Muller, O. F., DeLeon, A. C., Sher, L. D., Lemmon, W. M. and Kilpatrick, D. G. The use of an artificial pacemaker in the treatment of cardiac arrest and slow heart rates. *Circulation*, 120: 668, 1959.
46. Truex, R. C. and Bishop, J. K. Conduction system in human hearts with interventricular septal defects. *J. Thoracic Surg.*, 35: 421, 1958.
47. Kirklin, J. W., Harshberger, H. C., Donald, D. E. and Edwards, J. E. Surgical correction of ventricular septal defect: anatomic and technical considerations. *J. Thoracic Surg.*, 33: 45, 1957.
48. Bailey, C. P. and Fitch, E. A. The surgical treatment of ventricular septal defects. In: Cyclopedia of Medicine. (In press.)
49. Effler, D. B., Kolff, W. J. and Groves, L. K. Complications peculiar to open heart surgery. *Surgery*, 45: 149, 1959.
50. Truex, R. C. and Kain, J. A. Conduction tissue of anomalous human hearts. *Anat. Rec.*, 124: 472, 1956.
51. Allen, P., Lederman, J. J. and Pearl, G. J Prevention of surgical heart block by the use of supravital stain. *J. Thoracic Surg.*, 38: 57, 1959.
52. Kolff, W. J., Effler, D. B., Groves, L. K., Hughes, C. R. and McCormack, L. J. Pulmonary complications of open heart operations: their pathogenesis and avoidance. *Cleveland Clin. Quart.*, 25: 65, 1958.
53. Sirak, H. D. and Hosier, D. M. Creation of a temporary artificial ductus for the surgical correction of ventricular septal defects associated with severe pulmonary hypertension. *J. Thoracic Surg.*, 37: 1, 1959.
54. Swan, H., Maresh, G., Johnson, M. E. and Warner, G. The experimental creation and closure of auricular septal defects. *J. Thoracic Surg.*, 30: 542, 1954.
55. Blanco, G. Personal communication.
56. Bailey, C. P., Zimmerman, J. and Likoff, W. The complete relief of mitral stenosis: ten years of progress toward this goal. *Dis. Chest*, in press.
57. Benjamin, R. B., Flom, R. S., MacLean, L. D. and Lewis, J. J. The gradual closure of interatrial defects. *J. Thoracic Surg.*, 34: 679, 1957.
58. Lillehei, C. W. Discussion of paper presented by Sirak and Hosier. *J. Thoracic Surg.*, 34: 672, 1959.
59. Cooley, D. A. Personal communication.
60. Larios, R., Fitch, E. A., Blanco, G. and Bailey, C. P. The use of an artificial foraminal valve prosthesis in the closure of interatrial and interventricular septal defects. *Dis. Chest*, 36: 631, 1959.
61. Bailey, C. P. In: Gould, S. E. Pathology of the Heart, 2nd ed., p. 1020. Springfield, Ill., 1960. Charles C Thomas.

Historical Milestones

Sir William Broadbent on Pulseless Disease (1875)

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THE bizarre characteristics of "pulseless disease" and the advances which have recently been made in the treatment of that unusual ailment have directed attention anew to early descriptions of the disease.

Sir William Broadbent, K.C.V.O., M.D., F.R.S. (1835–1907), the author of the contribution which is reprinted herein, was a distinguished nineteenth-century clinician (Fig. 1). He studied medicine at Manchester and later was a pupil of Trousseau in Paris. His principal work in England was carried out at St. Mary's Hospital in London and at the London Fever Hospital. His clinical interests included neurology as well as cardiovascular disease. The prototype of the high-principled humane British physician, he became known as the father of the fatherless and the afflicted. His great merits were recognized by his appointment as physician to the royal family and by his elevation to the baronetcy.

Broadbent's article is titled "Absence of Pulsation in Both Radial Arteries, the Vessels being full of Blood." It appeared in the *Transactions of the Clinical Society of London*, volume 8, pages 165–168, 1875.

* * *

BROADBENT ON ABSENT RADIAL PULSATION

Henry H., aet. 50, a labourer, was admitted into St. Mary's Hospital May 2, 1874, suffering from ascites and bronchitis with emphysema. He had been at one time a sailor, had lived intemperately, and had had syphilis, but for many years had been steady and temperate.

Paracentesis abdominis was performed three times; last on June 3; and as after this there was no evidence of reaccumulation of fluid, and the bronchitis was cured, he was allowed to leave the hospital at his own wish.

He returned again on June 25, with recurrent ascites, and remained in the hospital till January 25, 1875, when he insisted on going home to die. He had been tapped in all fourteen times, and various methods of treatment had been tried for the relief of the ascites, which was due to cirrhosis of the liver.

The interest of the case consisted in the peculiarity of the circulation in the upper extremities, to be described.

There was no pulse at either wrist, but while this was the case the radial arteries could be distinctly felt full of blood. They could be rolled under the finger and followed for some distance along the fore-arm. That the round cord-like object under the fingers was really the radial artery was shown by the fact that when the arm was raised the blood receded, and the artery collapsed and became imperceptible. It should be added also, that from time to time, during the six months in which the case was under observation, a faint flickering pulsation could be detected, more frequently and more perceptibly in the left than the right radial. The flow of blood through the veins of the back of the hand and the fore-arm was vigorous, and the hands were warm and presented no appearance of languid or deficient circulation. The muscular condition of the extremities was good.

An additional interest was imparted to the condition by the statement of the patient that the absence of pulse had been detected (had come on, he said) after he had been thrown from a train in the Boxmoor tunnel thirty years before.

On further investigation pulsation was found to be absent in the brachial and subclavian arteries; present in the left carotid, and feebly in the right; vigorous in the femorals and posterior tibials.

The heart was covered by the emphysematous left lung, and its impulse was feeble; but the sounds were normal, and were heard at the usual situations. No dulness could be detected in the upper part of the chest, and there was no abnormal pulsation here or in the neck; no murmur, no intensification of the aortic second sound. No evidence, in fact, of aneurism or of intra-thoracic tumour. The patient's voice was high-pitched and squeaky, but this was natural to him.

I was unable to frame, or to obtain from physicians who saw the patient, any explanation of the phenomena described, or to find recorded cases throwing light upon them. I have more than once, in intra-thoracic aneurism, met with a similar condition of the circulation—a full artery, with little or no pulsation—in one or other arm, and found it explained after death by a valvular communication of the innominate or subclavian with the sac. In constriction of the aorta again, universal pulselessness has been described, but I could not apply these observations to the case of absence of pulse in both subclavians with good pulsation in the femorals and the left carotid, especially as I supposed the similar condition in the two subclavians to be due to a single cause.

It was in the hope of obtaining a solution to the problem that I kept the patient so long in the hospital, when at the last moment he insisted on going home to die, which he did within a week of his leaving, and before I had ascertained the name of the medical man under whose care he had placed himself. Fortunately, however, this was my friend, Dr. Hermann Jones, who sent the widow to me and enabled me to secure a post-mortem examination, of which the following is an account:

Heart. Right ventricle enlarged; no valvular disease; structure fairly healthy.

Aorta appeared slightly enlarged, but not otherwise altered when first exposed; removed for examination, together with a considerable length of the branches rising from the arch, the dissection being made with great care; no obvious abnormality apparent.

When laid open very little disease was found in the internal coat of ascending part of arch, and the walls were perfectly elastic. It was now seen, however, that the orifices of the innominate and left carotid arteries were close together, and that the mouth of the former was exceedingly small. On further examination the innominate was found not only to be narrowed at its origin, but rigid. An atheromatous patch surrounded the mouth of the vessel involving the structures both of the aorta and the innominate; it was hard and brittle without being distinctly calcareous, and separated readily from the outer tunic. Immediately above its origin the innominate enlarged to its usual size, and possessed its normal elasticity. Here, then, was the explanation of the absence of pulse, with a full vessel at the right wrist.

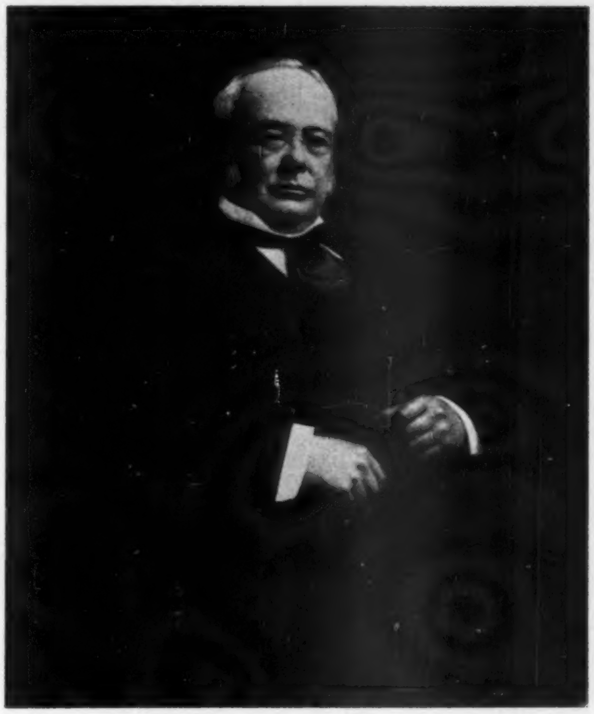

FIG. 1. Sir William Broadbent (1835–1907). From: Broadbent, M. E. The Life of Sir William Broadbent, Bart., K.C.V.O. London, 1909. John Murray.

Pursuing the examination, it was found that the left vertebral artery, instead of arising from the subclavian, sprang from the arch of the aorta close to the origin of the subclavian, the orifice of which was narrowed to the size of a crowquill by the proximity of the vertebral. Here again atheroma had invaded the constricted orifice and rendered it rigid, while the artery beyond was healthy and of full diameter. The absence of pulsation in the two radials, instead of being due to a single lesion, was thus caused by a repetition of a precisely similar condition at two separate points.

It will be at once seen how a constriction of the mouth of each of the two arteries with a larger elastic part beyond would neutralise the pulsatile movement of the blood. The narrowed communication would cut off the arteries from the general expansile movement of the aorta, as it would only permit of the passage of a small stream of blood insufficient to distend them; this stream, again, would be rendered more or less continuous by the pressure of the aorta on its contents, and any inequality in the propulsion would be further diminished by the large elastic part of the vessel, on the same principle as the second elastic ball in the ordinary spray-producing apparatus.

There are one or two other interesting points worthy of remark. The peculiarity had its source in a slight abnormality of the origin of the branches of the aorta, the approximation of the left carotid to the innominate, and the origin of the left vertebral directly from the arch of the aorta, close to the left subclavian. This is not uncommon, but it has not hitherto been known to give rise to narrowing of the orifices. In a smaller degree such a narrowing might give a pulse-trace simulating aortic stenosis.

Again, the occurrence of atheroma in an advanced stage at the narrowed orifices, while it was almost entirely absent elsewhere, illustrates the effects of strain in producing disease of the coats of arteries. There must always be additional strain where the cylinder of the aorta is pierced to give off branches, and the bloodstream is diverted, and atheroma is developed here earlier as a rule than elsewhere, but the constriction must have greatly increased the strain, just as there is a more rapid current and greater wear and tear of the banks at a narrow part of a river, and must therefore have been the cause of the unusually advanced atheroma at the orifices.

The remaining post-mortem appearances may be briefly enumerated. Pleura, generally adherent by fine connective tissue.

Lungs, emphysematous.

Liver small; capsule thick, opaque, and white; surface only slightly irregular near anterior edge; and on section liver substance pale, and not subdivided as in ordinary cirrhosis.

Spleen small; capsule thickened and opaque.

Kidneys about normal size; surface coarsely granular, and capsule adherent; cortex not greatly wasted.

* * *

Comments

The preceding text has distinct charm, which is due to the restrained wording and dignified tone. Indeed the description reminds us of Victorian novelists such as Trollope. The patient "had been a sailor, had lived intemperately, and had had syphilis." He had once been thrown from a train in the Boxmoor tunnel. In the inelegant jargon of twentieth century sociology, he had suffered the intoxications, infections and traumas which tend to be statistically characteristic of the underprivileged. After years of debauchery the patient had become steady and temperate, and perhaps had been a source of comfort to nineteenth-century English ladies interested in the reform of the working classes. The patient's ultimate entry into the ranks of the virtuous did not save him from recurrent ascites and more than a dozen paracenteses. The wages of sin proved to be, *inter alia*, the trocar.

As Broadbent says, the interest of the case consists in the peculiarity of the circulation in the upper extremities. Aspects of the patient's story which do not bear upon this problem are accordingly reduced to a minimum. The result is a concise uncluttered presentation.

Not content with the negative observation of absent radial pulse, Broadbent recognized that the radial arteries, although non-pulsatile, could be felt to be full of blood. This was confirmed by observations made when the patient's arms were elevated. At such times the radial arteries collapsed and became imperceptible. Occasionally a flicker could be felt at either wrist, especially the left wrist. Broadbent recognized moreover that the arterial blood supply to the hands was adequate despite the absence of pulses, and that the venous return was normal.

The study was extended to include the main pulses in all parts of the body. Broadbent found that the brachial and subclavian pulses were absent, the left carotid pulse present, and the right carotid pulse feeble, while the femoral and posterior tibial pulses were vigorous.

Since no abnormal dullness could be discovered in the upper part of the chest and there was no abnormal pulsation in the chest or neck, and murmurs were absent, Broadbent believed he had excluded the possibility of aneurysm and intrathoracic tumor. He therefore could not explain the physical signs and he was obliged to await clarification by autopsy.

The principal anatomical findings were: (1) narrowing of the innominate artery by an ostial

plaque; (2) similar ostial stenosis of the left subclavian artery; (3) anomalous origin of the left vertebral artery from the aorta and (4) abnormal proximity of the ostia of the innominate and left common carotid arteries. While these findings, especially the two first mentioned, explain the physical signs, Broadbent wondered whether or not the anomaly in the origins and locations of the arteries might have predisposed to the formation of plaques.

Such was Broadbent's simple but impressive contribution to our knowledge of "pulseless disease." The reader who wishes to study the later developments, including the surgical treatment, will find an abundance of information in the paper by De Bakey and his collaborators.*

ACKNOWLEDGMENT

Photograph by courtesy of Messrs. Elliott and Fry, Ltd., London, England.

* De Bakey, M. et al. Segmental thrombo-obliterative diseases of aortic arch. *J. A. M. A.*, 166: 998, 1958.

The Medical Use of Scales

An Historical Remark

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There is no doubt that ancient physicians realized the frequent association of obesity and certain symptoms, such as shortness of breath, symptoms of gout or cerebral hemorrhage as well as the association of other symptoms of the patient. It might be of interest to mention a few of the early applications of the scale as an instrument in medicine.

It is generally supposed that the first to have introduced the scale into medicine was the Italian, Santorio Santorio (1561–1636), professor at the Medical School in Padua, and a leader of the so-called iatro-physical school. His studies of insensible perspiration by weighing human beings is generally known. He is regarded by Castiglione as having introduced quantitative studies into medicine although balances had been utilized by governments as instruments of commerce prior to this time. The city of Cologne, a mediaeval center of commerce, had weight masters of the city, and Paris had so-called "Peseurs Publiques" as Government Officials, responsible for all matters connected with weights and balances in commerce.

By the eighteenth century scales were in full use. The Abbé Jaubert complained that in 1764 the act of weighing oneself was so popular in Paris that it was responsible for the appointment of a special weight master. He also reports that in his time a chapel under the name La Balance existed. This name came from ancient times, when in this monastery a big balance was kept on which sick people were weighed to determine whether their disease was improving or becoming worse. This balance was regarded by some as a miracle. However, Jaubert concludes his report with the opinion that it may have been this clinically used balance which gave Sanctorius the idea to use a balance for his famous experiments.[1] Therefore, at least in the opinion of Jaubert, the practice of weighing patients in the monastery preceded Sanctorius' discoveries and his introduction of quantitative methods into clinical and theoretical medicine.

Reference

1. Abbé Jaubert. Dictionnaire Raisonne Universel des Arts et Metiers (First Edition, 1764). Nouvelle edition, Paris, 1773.

Report on Therapy

Treatment of Atrioventricular Block with Prednisone*

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IT has been known for some time that the administration of glucocorticoids and ACTH shorten the P-R interval of the electrocardiogram.[1] By analogy, short P-R intervals are found in Cushing's syndrome while longer ones are observed in Addison's disease.[2] These observations led us to a trial of glucocorticoids in the treatment of A-V blocks, irrespective of their type or degree. This treatment had been previously attempted in cases of complete A-V block following myocardial infarction.[3]

MATERIAL AND METHODS

Among the several glucocorticoids, prednisone was chosen (occasionally prednisolone) as the hormone having fewer side effects. In a few cases, ACTH and cortisone were administered for various reasons and their effects were also studied. Thirty-one patients were treated by this method. They were classified as follows:

Grade 1 A-V block (ten patients): The majority had Chagas, myocarditis, while the others suffered from arteriosclerotic, metabolic or allergic heart disease.

Partial A-V block (two patients): One presented a hypertensive nephrogenic cardiopathy, the other had Chagas' disease; both had a 2:1 block.

Complete A-V block (intermittent) (seven patients): The majority suffered from arteriosclerotic heart disease.

Complete A-V block (permanent) (twelve patients): These patients had either arteriosclerotic heart disease or Chagas' disease.

All patients with rheumatic heart disease were excluded. The average dosage of prednisone was 40 mg. given daily, as smaller amounts of the drug proved ineffective. Larger dosages, up to 100 mg. daily, were tried without advantage.†

† In one case, studied after submission of this manuscript, a single dose of 40 mg. was given intramuscularly.

RESULTS

Grade 1 A-V Block: Seven of the ten patients showed disappearance of the block (Fig. 1). Two patients, who did not improve, had previously received a full dose of digitalis. The third patient who did not respond to the treatment had diabetes and hypoproteinemia. In

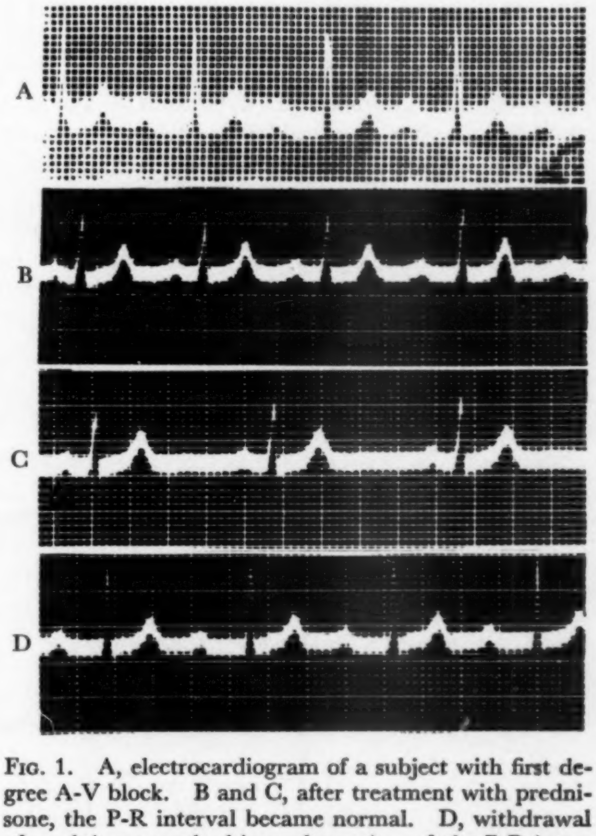

FIG. 1. A, electrocardiogram of a subject with first degree A-V block. B and C, after treatment with prednisone, the P-R interval became normal. D, withdrawal of prednisone resulted in prolongation of the P-R interval.

* From the Hospital Santa Casa de Misericordia, São Paulo, Brazil.

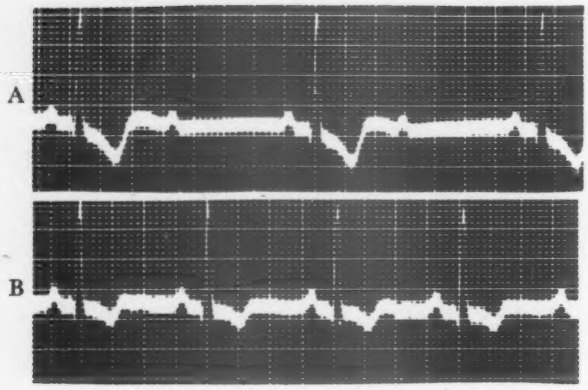

FIG. 2. A, electrocardiogram (lead II) of a subject with 2:1 A-V block. B, A-V conduction becomes normal following administration of prednisone.

three patients, normal rhythm persisted for several months after withdrawal of the drug while the other patients presented a recurrence of the disturbance. In the majority of patients, a period of variable P-R intervals preceded the normalization of the electrocardiogram.

Partial A-V Block: There was normalization of the electrocardiogram in both patients two days after the onset of the treatment (Fig. 2). The patient with renal hypertension maintained a normal rhythm for one and a half years until death resulted from renal failure. The patient with Chagas' myocarditis presented a grade 1 A-V block after the end of the treatment, and this mild disturbance persisted in spite of subsequent treatments.

Complete A-V Block (Intermittent Type): Complete disappearance of the block occurred in five of the seven patients treated (Fig. 3). Two patients have been followed up for two years. In all seven patients, the block was caused by coronary disease and in one there was also mild diabetes. In one patient, an elderly hypertensive and diabetic woman, the disappearance of the block was of short duration and further therapeutic trials failed to bring any improvement. Another similar patient, receiving digitalis therapy, failed to improve at all.

Complete A-V Block (Permanent Type): There was no electrocardiographic improvement in any of the twelve patients except for an increase of the atrial and ventricular rates during the period of treatment.

COMMENTS

All patients showed some general improvement and two (first degree A-V block) had decrease of the signs of heart failure (one had Chagas' myocarditis).

The Q-Tc was measured in patients with first degree A-V block, and it was noted that there was a parallel abbreviation of both the P-R interval and the Q-Tc (Fig. 4). However, in patients with severe blocks, the Q-Tc was but slightly affected by treatment, or not at all.

The positive results obtained in patients with partial or complete A-V block occurred only when the disturbance was intermittent, indicating that the block was due to a predominantly functional mechanism. The positive results were obtained as soon as the treatment was initiated: therefore, it is superfluous to prolong therapy if improvement does not occur in the first four or five days. A gradual withdrawal of the drug is also unnecessary.

It is likely that the mechanism of action is the

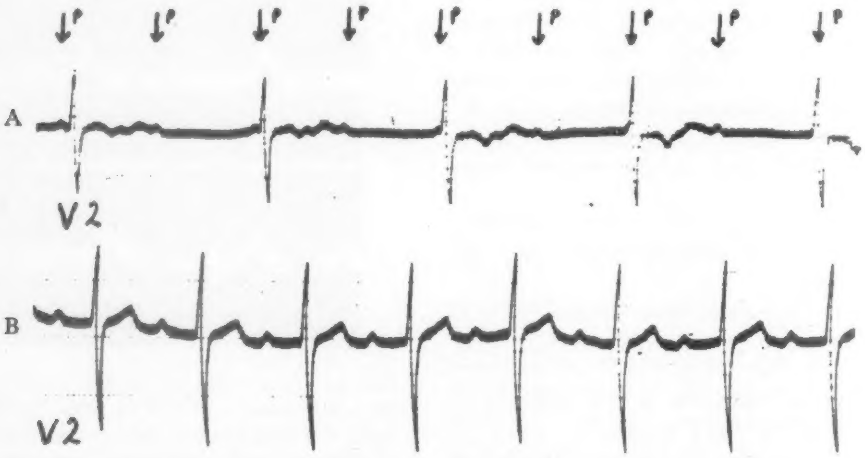

FIG. 3. A, electrocardiogram (lead V_2) of a subject with complete (intermittent) A-V block. B, after administration of prednisone, the atrial beats are conducted but there is prolongation of the P-R interval (first degree block).

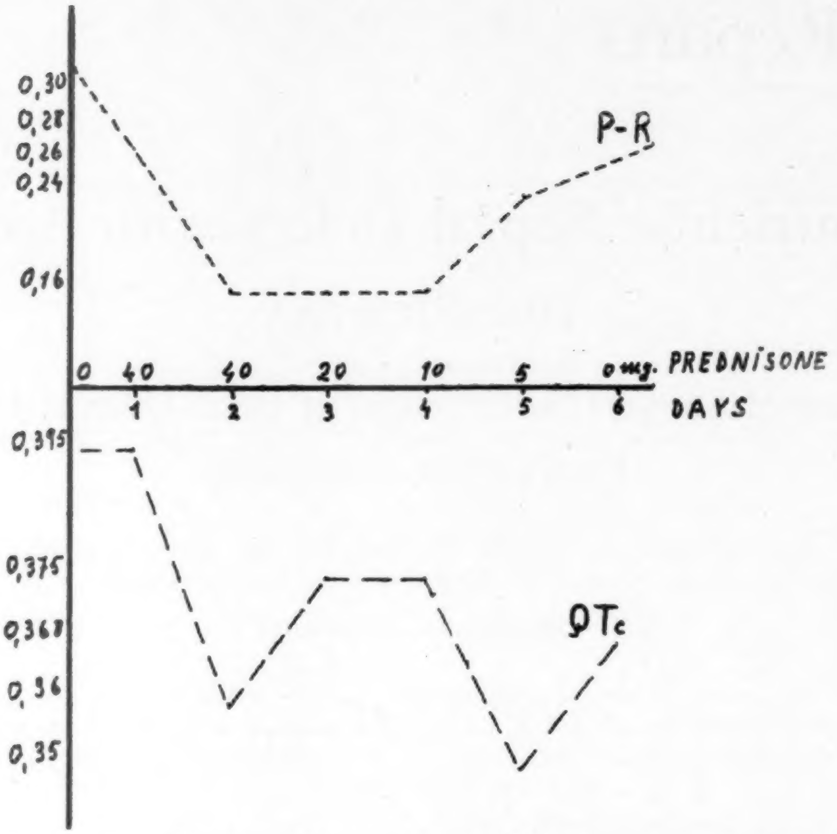

FIG. 4. The effect of prednisone on Q-Tc and P-R interval in patients with first degree A-V block. There is a grossly similar shortening of both P-R and Q-Tc intervals. Average results in ten patients with A-V block.

following. The glucocorticoids act upon the areas of edema which surround the A-V node and decrease its severity. (This edema has been found in postmortem examination.)[2,5] The excitability of the A-V node is increased by administration of the drug, as shown by the changes of the P-R interval during treatment with glucocorticoids and also in patients with Addison's or Cushing's disease.

It is possible that therapeutic success obtained by various other treatments is due to formation of glucocorticoids through stress, or to physiological stimulation of the A-V node (sympathomimetic drugs).[7]

SUMMARY

Prednisone has been used in thirty-one patients with A-V block. Prednisone reduced the P-R interval in seven of ten patients with first degree block. Two patients with incomplete and intermittent A-V block were successfully treated with prednisone. Five of seven patients with complete but intermittent A-V block were also successfully treated. In twelve patients with complete and permanent block, only a moderate increase of the ventricular rate was observed

REFERENCES

1. LEPESCHKIN, E. Modern Electrocardiography. Baltimore, 1951. Williams & Wilkins.
2. LOWN, B., ARONS, W. L., GANONG, W. F., VAZIFOAR, J. P. and LEVENE, S. A. Adrenal steroids and auriculoventricular conduction. *Am. Heart J.*, 50: 760, 1955.
3. PRINZMETAL, M. and KENNAMER, R. Emergency treatment of cardiac arrhythmias. *J. A. M. A.*, 154: 1049, 1954.
4. JOOSSENE, J. V., DE WITTE, P. E. and KESTELOOT, H. Action favorable de la prednisone dans un syndrome d'Adams-Stokes. *Acta cardiol.*, 12: 661, 1957.
5. LITCHFIELD, J. W., MANLEY, K. A. and POLAK, A. Stokes-Adams attacks treated with corticotrophin. *Lancet*, 1: 935, 1958.
6. CARAMELLI, Z. et al. First results of the treatment of the A-V block with prednisone—Preliminary note presented to "Associatiacão Paulista de Medicina," September 1957. *Arch. brasil. cardiol.*, 11: 109, 1958.
7. LENGYEL, L., SAPIENZA, P. and CARAMELLI, Z. Comparaison des effets du sulfate d'amphétamine, de l'adrénaline et de l'ACTH sur la chute éosinophilique dans le sang circulant. *Semaine hôp. Paris*, 33: 65, 1957.

Case Reports

Ventricular Septal Defect with Aortic Insufficiency

Successful Surgical Correction of Both Defects by the Transaortic Approach*

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CONGENITAL ventricular septal defect with aortic insufficiency was reported by Breccia[1] in 1906. A review of the subject was recently reported in this Journal by Scott et al.,[2] who collected twenty-one cases established at autopsy; cited references for ten additional cases diagnosed by cardiac catheterization, angiography, or exploratory thoracotomy; and also added seven of their own cases, two confirmed at autopsy. Fifteen other cases are mentioned with less conclusive data.[3–6] Three additional cases have been reported by Denton and Pappas,[7] one of which was verified at autopsy, another by surgery and a third by catheterization.

We recently studied a thirteen year old girl considered to be suffering from free aortic insufficiency. Her ventricular septal defect was not diagnosed preoperatively. Planning correction of the aortic valve defect as described by Garamella[9–12] and also clinically applied by Bailey,[13] surgery was performed by the transaortic approach. Aortic cusp subluxation with high ventricular septal defect was found. Both lesions were corrected with remarkable improvement in the patient's condition. The experiences leading to our fortuitous result may be helpful in the recognition of this condition. Successful surgical correction of both lesions by the transaortic approach has not been reported. Two earlier alternate attempts proved unsuccessful.[7]

CASE REPORT

A thirteen year old girl (No. 55274) was admitted to Mount Sinai Hospital, Minneapolis, on October 27, 1957. A heart murmur had been present since birth. She was admitted for cardiac evaluation. The patient's activities had not been restricted. She had had no symptoms except for slight shortness of breath on moderate exertion. She kept up with her age group in school. There was no history of squatting, cyanosis, edema, pain in the chest or hemoptysis.

Clinical Findings in First Admission: The patient was in no distress and was normally developed for her age. Blood pressure ranged between 140 to 160 mm. Hg systolic, and 2 to 20 mm. Hg diastolic. The lungs were clear. The heart was enlarged to the left. There was a heaving apical impulse. A systolic thrill was palpable at the base. Grade IV systolic and diastolic murmurs were heard over the base of the heart radiating down the left sternal border to the apex. The systolic murmur could also be heard in the vessels of the neck and in the arms. A normal second sound was heard at the base. No clubbing or cyanosis were noted.

The electrocardiogram (Fig. 1A) showed very tall R waves and depressed S-T segments in leads II, III and aVF and a negative T in III and aVF.

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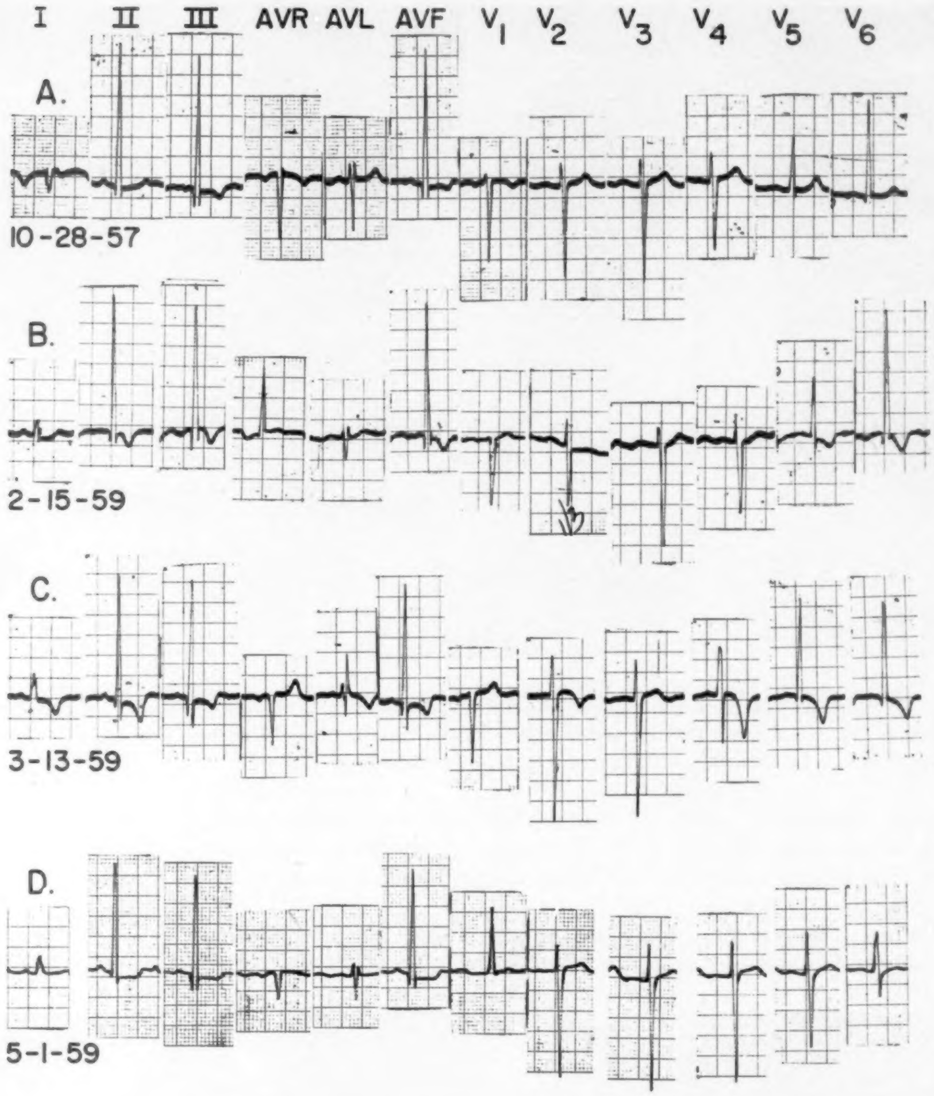

FIG. 1. Two preoperative and two postoperative electrocardiograms. A, electrocardiogram on first admission showing vertical heart position. B, second admission, preoperative electrocardiogram, showing negative T waves in leads II, III, aVF, V_5 and V_6, interpreted as left strain in a vertical heart and digitalis effect. The axis is shifted slightly to the left. C, electrocardiogram two weeks postoperative showing extreme T wave changes in limb leads and left-sided chest leads. D, two months postoperative electrocardiogram showing return to a nearly normal pattern.

Cardiac fluoroscopy and radiography (Fig. 2A) showed marked cardiac enlargement, predominantly left ventricular, with tremendous pulsation of the ascending aorta. No valvular calcification was noted. Pulmonary overcirculation was not seen. Catheterization of the right heart was performed on October 28, 1957 by Dr. John LaBree (Table I).

The patient was thought to have rheumatic heart disease with aortic insufficiency and aortic stenosis.

Clinical Findings in Second Admission: She was lost to follow-up studies until her second admission fourteen months later on February 13, 1959. In the interim her condition had rapidly deteriorated and

TABLE I

Cardiac Catheterization Findings on October 28, 1957

Site Measured	Pressure (mm. Hg)	O_2 Saturation (%)
Pulmonary artery	20/10	72
Right ventricle	20/2	72–71
Right atrium	5/1	66–68
Superior vena cava	. . .	75–68
Femoral artery	. . .	100

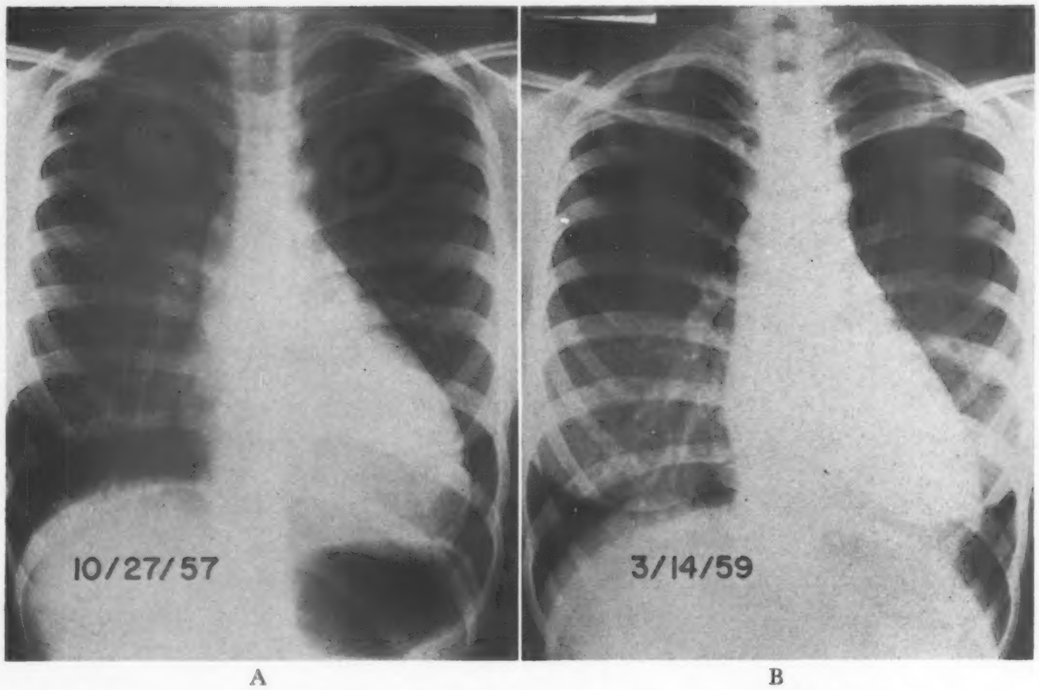

FIG. 2. Posteroanterior roentgenograms of the chest. A, first admission, showing enlargement of the heart, straightening of the left border and normal lung fields. B, second admission, two weeks postoperative, showing considerable reduction in heart size.

extreme dyspnea developed which prevented her from entering school in the fall of 1958. Dyspnea and orthopnea produced complete invalidism by November 1958. Since December 1958 the patient slept poorly because of extreme nocturnal dyspnea and at this time digitalization was commenced. Some improvement in breathing followed but she remained bedridden. Moderate pedal edema became apparent in January 1959.

She weighed 100 pounds, about fifteen pounds less than normal; height was 5 feet 3 inches. Pulsation of the retinal arteries was a prominent finding.

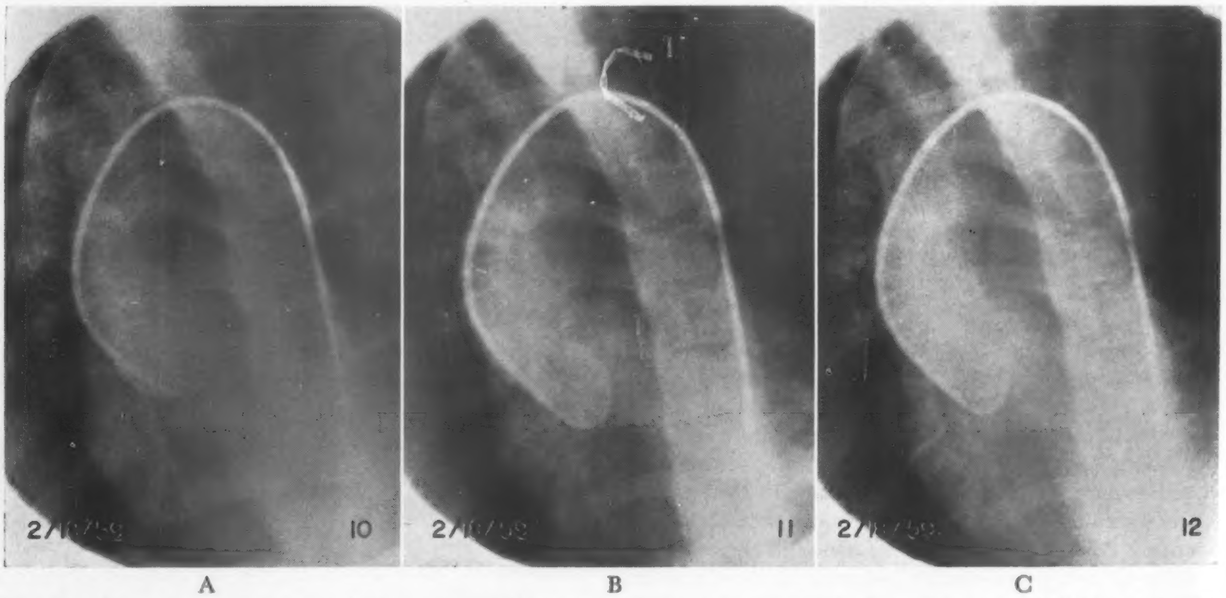

FIG. 3. Three exposures taken during retrograde aortography, being the tenth, eleventh and twelfth in serial radiography at three exposures per second. A, exposure 10. Catheter tip of sinus of Valsalva with early filling of aorta and massive regurgitation into the left ventricle. B, exposure 11. Aorta is well filled with contrast dye outlining cusps. Opacification of aorta and left ventricle. C, exposure 12. Further delineation of aorta from cusps to the arch including great vessels; left ventricle well filled; no filling of right ventricle.

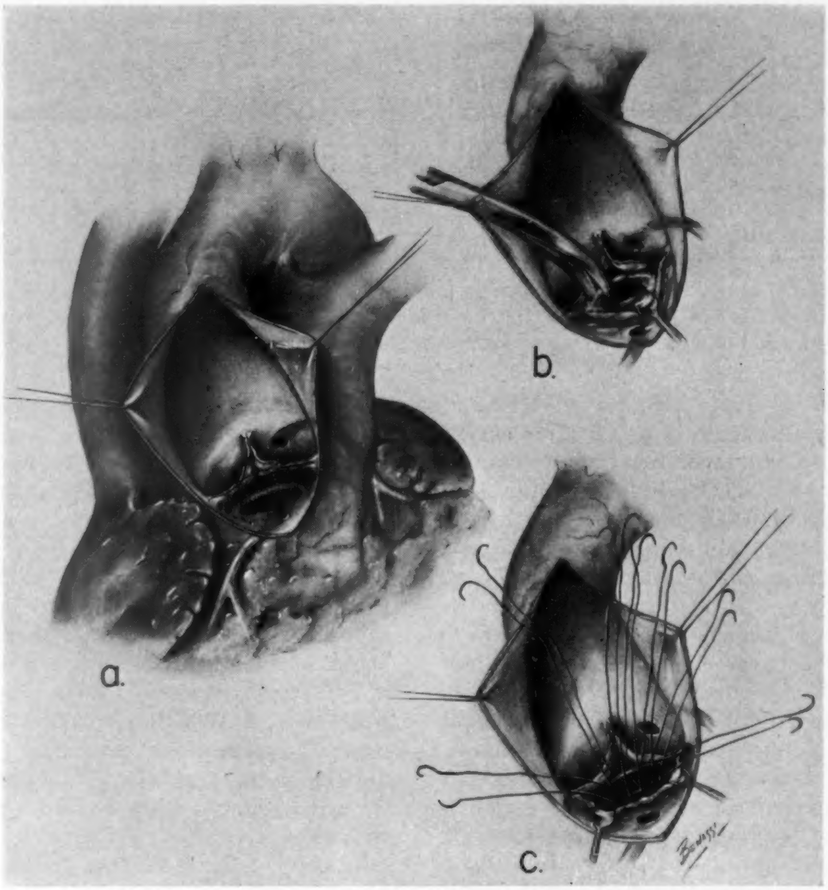

Fig. 4. Drawing of pathologic anatomy and surgical correction of aortic insufficiency and ventricular septal defect: (a) aortotomy showing the enlarged and prolapsed right cusp overriding the high ventricular septal defect; (b) the right cusp is elevated showing the ventricular septal defect and the division of adhesions on the undersurface of the right cusp; (c) closure of ventricular septal defect with interrupted silk sutures.

The vessels of the neck showed tremendous collapsing pulsation of free aortic insufficiency. The physical findings of the heart were as noted previously, except that both the systolic and diastolic murmurs now were accompanied by thrills over the left second and third interspaces. Both murmurs were maximal there and were transmitted all over the chest. Blood pressures were difficult to obtain because a systolic sound could be heard in the antecubital space with maximal cuff pressure but at 140 mm. Hg there was a change suggesting the beginning of Korotkov's sounds. Palpatory systolic pressure was 150 mm. and diastolic pressure varied from 0 to 10 mm. The lungs were clear. The liver and spleen were not palpable. A Duroziez murmur and Corrigan pulse were obvious. Capillary pulses could be shown easily in the lips and nail beds. The head nodded with each systole. The mattress and bed vibrated rhythmically with the cardiac pulsations.

The serologic test for syphilis was negative. Blood findings included: hemoglobin, 12 gm., white blood count, 6,300 per cu. mm. with 64 per cent polymorphonuclear cells, 31 per cent lymphocytes and 5 per cent eosinophils; sedimentation rate, 31 mm. per hour. Urinalysis revealed no abnormalities. Several blood cultures were negative. The electrocardiogram (Fig. 1B) showed negative T waves now apparent in leads II and III, V_5 and V_6 with a positive T wave in aVR. This was interpreted as left ventricular strain in a vertical heart and digitalis effect. X-ray of the chest and cardiac fluoroscopy showed findings similar to those of the previous examinations.

On February 18, 1959 a retrograde aortogram showed reflux of dye from the aorta into the left ventricle (Fig. 3). No evidence for shunting into the pulmonary artery or right ventricle could be demonstrated. With the diagnosis of congenital aortic insufficiency surgery was performed on February 27, 1959 using total cardiopulmonary bypass with hypothermic cardiac arrest and direct coronary perfusion.

DESCRIPTION OF OPERATION

The chest was entered through a sternal splitting incision. The pericardium was opened vertically

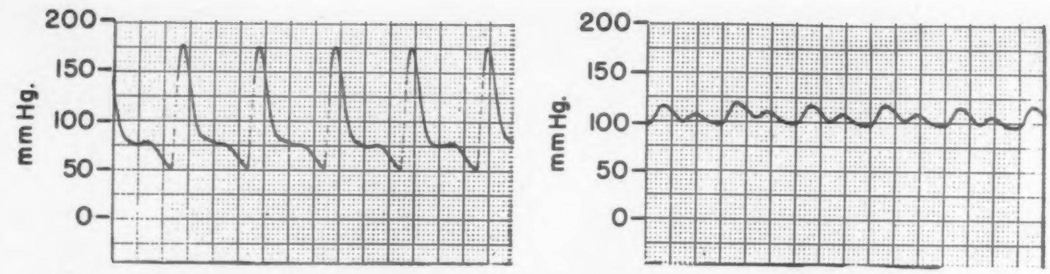

FIG. 5. Radial artery pulse curve showing preoperative (left) blood pressure 175/50 and postoperative (right) blood pressure 115/100 mm. Hg. The postoperative tracing appears damped but the restoration of a more normal dicrotic notch and wave is apparent.

after reflecting the thymus. Striking pulsations of the aorta with alternate blanching and pinking during systole and diastole were noted. An intense diastolic thrill was palpable over the base of the aorta. The patient was heparinized, 1.5 mg. per kg. of body weight, and cannulations of the right femoral artery, superior and inferior venae cavae, right and left atria were performed. Total cardiopulmonary bypass was conducted utilizing a disc oxygenator.[14] Flow rates ranged between 50 to 60 cc. per kg. per minute. The aorta was cross clamped. A no. 12 F. catheter was inserted into the base of the aorta for perfusion of the coronary arteries with hypothermic blood. Perfusion at a rate of 100 to 500 cc. per minute was continued until cardiac arrest occurred in three minutes. Cooling was accomplished by circling the blood through a water bath of 5 to 12°C. as described by Cross[15] and Long.[16] Ventricular fibrillation followed.

Aortotomy was started on the anterolateral aspect and carried laterally opposite the non-coronary sinus. Inspection showed asymmetry of the aortic valve cusps, the left being the smallest and the right the largest.* The right cusp was prolapsed into the ventricular cavity. The mid-portion of the convex ventricular surface of the right cusp was adherent to the septal myocardium below the aortic valve. With further inspection and dissection of the undersurface of the right cusp, the basic pathologic disorder was encountered: a high ventricular septal defect approximately 3 cm. in greatest diameter (Fig. 4). The aortic insufficiency was evidently caused by the dislocation of the right cusp. This leaflet was found to be attached to the inferior rim of the septal defect. This margin was mostly muscular with a 2 to 3 mm. fibrous edge. Sufficient tissue in the superior rim of the ventricular septal defect permitted anatomical closure with eight 3-0 sutures without undue tension. Because the right cusp was elongated plication was carried out to even the length of the free margin. The two commissures adjacent were reinforced with two 4-0 silk sutures. During these reparative procedures the coronary arteries were directly cannulated and perfused twice with cold blood at nine minute intervals following the initial cardiac arrest.

Before closing the aorta the coronary arteries were again perfused directly with warm blood and cardiac action was readily re-established. The aortic wound was closed and the aortic cross clamp removed. Ventricular fibrillation recurred. Resuscitative efforts were carried out for a fifteen minute period. Defibrillation was ultimately achi-ved with four consecutive electric shocks (200 volts, 1.5 to 3 amps., 0.1 second). Heart action remained regular and forceful. Cardiac bypass was terminated and decannulations performed. The mediastinum was drained with two catheters and the sternum approximated with braided wire. Data relating to cardiac bypass are found in Table II and Fig. 5.

Course: The postoperative course was uneventful and the patient was discharged sixteen days later. She was ambulatory and without dyspnea. Her blood pressure was 150/86 mm. Hg. A grade III systolic and a grade II diastolic murmur were heard at the base with no accompanying thrills. The peripheral findings of aortic insufficiency had disappeared.

The patient has returned to high school and four months postoperatively has resumed physical ac-

* The left and right aortic valve cusps refer to the valve leaflets corresponding to the left and right coronary ostia; the posterior is the non-coronary cusp.

TABLE II
Data Pertaining to Cardiac Bypass Procedure

Factor	Preoperative	Postoperative
pH (arterial)	7.4	7.59
Plasma hemoglobin (mg. per cent)	(not carried out)	127
Blood pressure (mm. Hg) (Fig. 5)	175/50	120/100
Total perfusion flow rate (cc./kg./min.)	2,100–2,500 50–60	...
Coronary perfusion (cc./min.)	100–500	...
Perfusion time (min.)	60	...
Period of cardiac arrest (min.)	30	...

tivity including one of her hobbies, horseback riding.

Comments

The clinical features of this case fit well with previously reported cases of ventricular septal defect with aortic insufficiency and include: (1) Almost continuous aortic systolic and diastolic murmurs; (2) wide pulse pressure; and (3) peripheral signs of aortic insufficiency. Our case is unique in that catheterization as performed and x-ray studies failed to show any evidence of a left-to-right shunt. The basis for the absence of a demonstrable shunt appeared to be the baffle effect of the herniated right cusp, the convex side of which was in part held by adhesions to the lower rim of the ventricular septal defect.

The differential diagnosis of the aortic incompetence includes those etiologies not associated with shunts such as: (1) rheumatic, syphilis or bacterial endocarditis, (2) aneurysm of sinus of Valsalva, (3) Marfan's syndrome, (4) trauma, (5) bicuspid aortic valve, (6) congenital fenestrations, (7) systemic arteriovenous fistula, (8) Paget's disease of bone, and (9) thyrotoxicosis; and those associated with shunts, namely, (1) patent ductus arteriosus, especially with interventricular septal defect or with acquired aortic insufficiency, (2) aorticopulmonic window, (3) ruptured sinus of Valsalva, (4) ventricular septal defect with acquired aortic insufficiency or with a bicuspid aortic valve, (5) coronary arteriovenous fistula, (6) truncus arteriosus, and (7) rupture of aortic aneurysm into the pulmonary artery or superior vena cava.

Pertinent features of the differential diagnosis have been well described by Scott[2] and Winchell.[17]

The nearly continuous systolic and diastolic basal noise in ventricular septal defect with aortic insufficiency has often led to the impression of a machinery murmur and the erroneous diagnosis of a patent ductus arteriosus.[2,17] The clinical findings associated with collapsing systemic pressure could also be assigned to a fall of aortic pressure through a large ductus. The murmurs of ventricular septal defect with aortic insufficiency, however, are not truly continuous being momentarily interrupted by the heart sounds. The murmur of the septal defect is entirely systolic with no tendency to override the heart sounds. Similarly, the murmur of the aortic insufficiency is precisely regulated within diastole fading before the first sound. The continuous murmur of blood flow through a patent ductus, independent of valve action, has no such exact relationship to heart sounds. The murmur increases in systole, decreases in diastole, and overrides the heart sounds producing the independent quality described as a machinery murmur. Another clinical point of differentiation is the extremely low diastolic pressure and high pulse pressure with attendant peripheral findings in this form of aortic insufficiency found to a degree not usual in patent ductus arteriosus.

Gross[4] has called attention to the intimate relationship of high ventricular septal defects to the "medial" aortic cusp. He suggested that the septal defect can contribute to the malposition of the aortic valve by absence of supporting tissue beneath the valve. Edwards[18] states that another contributing factor is the deviation of the aorta from its normal relationship with the ventricular septum.

The surgical correction of both the aortic insufficiency and ventricular septal defect by the transaortic approach, although successful in this instance could be managed by separate exposures in the aorta and right ventricle, if the ventricular septal defect were not readily accessible and reparable from above. Correction of both lesions from the ventricular approach would be more difficult since the pathologic anatomy of the aortic valve is less discernible and less accessible from the ventricular side. Moreover, attacking the ventricular septal defect before correction of the aortic insufficiency of this magnitude potentially introduces severe operative blood loss due to the aortic regurgitation unless measures are taken to cope with this problem.

Summary

1. A case of ventricular septal defect with aortic insufficiency due to prolapse of the right aortic cusp is reported.

2. Cardiac catheterization and x-ray studies failed to show evidence of a left-to-right shunt.

3. Surgery directed at correction of the aortic insufficiency by plastic repair of the aortic valve serendipitously revealed a ventricular septal defect and permitted successful repair of both defects by the transaortic approach.

References

1. Breccia, G. Sopra un caso di morbo del Roger complicato con insufficienza aortica, decorso senza sintomi. *Gazz. d. Osp. Milano,* 27: 625, 1906.
2. Scott, R. C., McGuire, J., Kaplan, S., Fowler,

N. O., Green, R. S., Gordon, L. Z., Shebatai, R., Davolos, D. D. The syndrome of ventricular septal defect with aortic insufficiency. *Am. J. Cardiol.*, 2: 530, 1958.
3. Dexter, L., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Sosman, M. C. and Evans, J. M. Studies of congenital heart disease. III. Venous catheterization as a diagnostic aid in patent ductus arteriosus, tetralogy of Fallot, ventricular septal defect and auricular septal defect. *J. Clin. Invest.*, 26: 561, 1947.
4. (*a*) Gross, R. E. The patent ductus arteriosus. Observations on diagnosis and therapy in 525 surgically treated cases. *Am. J. Med.*, 12: 472, 1952.
   (*b*) Gross, R. E. The Surgery of Infancy and Childhood. Philadelphia, 1953. W. B. Saunders Co.
5. Nadas, A. S. Pediatric Cardiology. Philadelphia, 1957. W. B. Saunders Co.
6. Becu, L. M., Fontana, R. S., DuShane, J. W., Kirklin, J. W., Burchell, H. B. and Edwards, J. E. Anatomic and pathologic studies in ventricular septal defect. *Circulation*, 14: 349, 1956.
7. Denton, C. and Pappas, E. G. Ventricular septal defect and aortic insufficiency. *Am. J. Cardiol.*, 2: 554, 1958.
8. Claypool, J. G., Ruth, W. and Lin, T. K. Ventricular septal defect with aortic incompetence simulating patent ductus arteriosus. *Am. Heart J.*, 54: 788, 1957.
9. Garamella, J. J., Anderson, J. G., Oropeza, R., Jensen, N. K., Hay, L. J., and Naidu, R. A new concept in the surgical treatment of aortic insufficiency. *Minnesota Med.*, 41: 260, 1958.
10. Garamella, J. J., Andersen, J. G. and Oropeza, R. The surgical treatment of aortic insufficiency by open plastic revision of the tricuspid aortic valve to a bicuspid valve. *Surg., Gynec. & Obst.*, 106: 679, 1958.
11. Garamella, J. J., Andersen, J. G., Oropeza, R., Veloso, A., Naidu, R. and Hay, L. J. Surgical treatment of aortic insufficiency by open plastic revision of the tricuspid aortic valve to a bicuspid valve. *S. Forum*, 9: 329, 1958.
12. Garamella, J. J., Andersen, J. G., Oropeza, R., Veloso, A., Naidu, R. The surgical treatment of aortic insufficiency by conversion of the tricuspid aortic valve to a bicuspid valve. Chronic experimental studies. *J. Thoracic Surg.*, 37: 177, 1959.
13. Bailey, C. P. and Zimmerman, J. The surgical correction of aortic regurgitation. Bicuspid conversion. *Am. J. Cardiol.*, 3: 6, 1959.
14. Kay, E. B. and Cross, F. S. Direct vision repair of intracardiac defects utilizing a rotating disc reservoir-oxygenator. *Surg., Gynec. & Obst.*, 104: 711, 1957.
15. Cross, F. S., Jones, R. and Berne, R. M. Localized cardiac hypothermia as an adjunct to elective cardiac arrest. *S. Forum*, 8: 355, 1957.
16. Long, D. M. Personal communication.
17. Winchell, P. and Bashour, F. Ventricular septal defect with aortic incompetence simulating patent ductus arteriosus. *Am. J. Med.*, 20: 361, 1956.
18. Edwards, J. E. Pathologic aspects of cardiac valvular insufficiencies. *Arch. Surg.*, 77: 634, 1958.

Aorticopulmonary Septal Defect

Diagnosis and Report of Case Successfully Treated*

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AORTICOPULMONARY septal defect is a rare congenital anomaly of the heart related to persistent truncus arteriosus and consisting of free communication between the ascending aorta and the adjacent main pulmonary artery. Various descriptive terms have been used for this anomaly. It has been referred to as a partial truncus, aorticopulmonary fistula and aorticopulmonary window. The fact that it simulates patent ductus arteriosus always raises the question of differential diagnosis whenever signs suggestive of patent ductus arteriosus are noted.

The prevalence of this defect can be estimated from the fact that in 1949 Collett and Edwards[1] mentioned thirteen case reports in their review and in 1956 D'Heer and van Nieuwenhuizen[2] referred to thirty-six cases in the literature. In an analysis of a thousand case reports of congenital cardiac defects Abbott[3] mentioned ten aorticopulmonary septal defects.

PATHOLOGY AND EMBRYOLOGY

The defect usually consists of an opening with its lower margin at the aortic valve ring or a few millimeters above it. Because of its embryologic origin it always occurs in the ascending portion of the aorta. It should not be confused with the window-type patent ductus arteriosus which occurs in the normal ductus position. Embryologically, the aortic septum is formed concomitantly with rotation of the heart, so that the aorta is placed to the left and posteriorly, and the pulmonary artery is placed to the right and anteriorly. If there is interference with fusion of a septum or if the heart rotates incompletely or not at all, we have the possibility of three defects: (1) interventricular septal defect; (2) persistent truncus arteriosus; and (3) aorticopulmonary septal defect.

In 1950 Downing[4] reviewed the postmortem findings and found right ventricular hypertrophy had been present in all the cases and left ventricular hypertrophy as well in approximately half the cases. This is to be expected as there is a tremendous flow into the pulmonary artery, and severe changes in the pulmonary arteriolar bed, as well as in the left atrium, may result.

CLINICAL FINDINGS

Cardiac Catheterization: The diagnosis is extremely difficult to make at times and on certain occasions may be made only by angiocardiography. Cardiac catheterization may be the only means of making a definitive diagnosis in this anomaly and is of value in several ways. First, the course which the catheter takes is of importance. In the case of an aorticopulmonary window, the catheter enters the aorta from the pulmonary artery and ascends into the innominate artery or the left common carotid artery. In the case of a patent ductus arteriosus, the catheter usually enters the descending aorta. This difference is of great diagnostic importance in distinguishing the two and, therefore, whenever there is a question of diagnostic importance, the patient should be placed in a lateral position under fluoroscopy in order to determine whether the catheter lies in the ascending or descending aorta. Blood oxygen studies may not be significant enough to distinguish between this defect and a ventricular septal defect and, therefore, should not be completely relied upon.

Angiocardiography: This will give the diagnosis

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TABLE I
Summary of Cardiac Catheterization Findings

Site	O_2 Content (vol. %)		Pressure (mm. Hg)	
	2/1/50	12/12/58	2/1/50	12/12/58
Superior vena cava	10.0	14.2	...	...
Inferior vena cava	...	15.0	...	...
Right atrium				
High	...	14.0	...	...
Mid	11.6	13.3	1 (mean)	5 (mean)
Low	...	15.0	...	...
Right ventricle				
Tricuspid valve	12.0	13.8	35/0	...
Mid	...	15.3	...	44/5
Outflow	12.0	15.0	35/0	...
Main pulmonary artery	13.5	16.4	13/5	20/8 (mean 12)
Right pulmonary artery	13.7	15.6	10 (mean)	...
Left pulmonary artery	13.3	15.7	18/9	23/12 (mean 18)
Arterial catheter in MPA	...	16.4	Simultaneously	17 (mean)
Venous catheter in MPA	...	16.2		17 (mean)
Right brachial artery	16.5 (99% sat.)	18.3 (95% sat.)	...	...
Capacity	16.9	19.6	...	...

in most instances and is best carried out as an aortogram by injecting the contrast medium in retrograde fashion into the brachial artery, or by threading a catheter up into the artery into the descending aorta and making the injection there.[5] It is necessary that the aortic valve area be visualized in order to outline the defect clearly. The aortogram will show a pulmonary artery and its branches filling from the aorta.

Electrocardiogram: The electrocardiographic pattern will depend upon the size of the defect. If the opening is large, right ventricular hypertrophy predominates with or without a pattern of left ventricular hypertrophy. If the opening is small, the record may be normal or a left ventricular hypertrophy pattern may occur, as in patent ductus arteriosus.

Murmurs: The most frequently recorded murmur is a systolic murmur followed by a diastolic murmur heard down the left sternal border. This is in a much lower location as compared to the patent ductus arteriosus murmur. In early infancy there may be no murmur at all and in some cases there may be a continuous murmur that is similar to that of a patent ductus arteriosus. As has been intimated, the diagnosis is not easy to make. An aorticopulmonary septal defect may be suspected when a continuous murmur is found below, or more central than, the usual point of maximum intensity that is present with a patent ductus arteriosus. Again, suspicion is aroused if there is a systolic-diastolic murmur down the left sternal border. In a great number of cases the diagnosis was made during thoracotomy for a presumed patent ductus arteriosus; in such cases the surgeon usually felt a thrill over the route of the pulmonary artery as it leaves the heart.

Dyspnea: Dyspnea is usually present and is apparent at rest or with mild exertion in severe cases. Although symptoms may be present at any age, they are usually present at an early age, since the loud murmur is recognized early.

Prognosis

The prognosis in the past has been poor, due to the high incidence of pulmonary artery hypertension. Actually, the prognosis in these cases is poorer than in patent ductus arteriosus. Downing[4] and associates have pointed out that the life-time of fourteen patients in whom diagnosis was confirmed at autopsy varied from three days to thirty-seven years.

Treatment

Surgery is indicated in these cases because of the high incidence of premature death. Successful surgery was first reported by Gross[6] in 1952 and subsequently periodic reports of occasional successful cases have appeared.[7–9] It is our belief that patients in whom there is no reversal of flow from the pulmonary artery to the aorta should be subjected to surgery.

Several anatomic features of the lesion account for the technical problem of surgical repair. Among these features is the fact that the fistula's communication does not have the consistency of a ductus arteriosus and, therefore, attempts to divide the fistula and repair the ends may compromise the diameter of the aorta or pulmonary artery and tearing of these vessels may result. The posterior wall of the fistula is extremely thin and this has been the cause of many deaths reported. Also, the presence of associated pulmonary hypertension increases the risk of the procedure because of the friability of the arterial wall. There is general agreement that division of the aorticopulmonary window is preferable to ligation because of the tendency for ligatures to cut through the vessel walls with resultant subsequent recanalization. It is also extremely difficult to ligate and completely close off a short communication. Therefore it is preferable to either treat this as a ductus under normothermic conditions and divide the structure between clamps and oversew each end; or with the aid of a pump oxygenator, divide the defect under direct vision and oversew each end. Oxygenated blood, in the meantime, is being served to the brain. Another approach would be the use of inflow occlusion with the aid of hypothermia and transection of the defect with oversew after that.

It is our preference, at this time, to have a pump oxygenator ready and then to proceed with the dissection of the defect. In the event that difficulty is envisioned, the patient should be placed on the pump oxygenator and the defect closed during cardiopulmonary bypass.

Case Report

A. P., an eleven year old boy, was admitted to The Mount Sinai Hospital for the first time in 1950 for evaluation of a cardiac murmur known to be present since infancy. He was a "blue baby" at birth, and had convulsive seizures and periods of cyanosis during the first few months of life. His growth and development in early life had been slow, but had been at a normal rate since then.

First Admission: The original physical examination in 1950 revealed a blood pressure of 96/50 mm. Hg. The point of maximal impulse was in the fifth intercostal space outside the midclavicular line. There was a grade 4/4 harsh machinery systolic-diastolic murmur heard best in the second and third intercostal spaces to the left of the sternum. The murmur radiated to the left and into the neck. Systolic and diastolic thrills were palpable over the areas where the murmurs were heard best. The second pulmonic

Fig. 1. Spot x-ray film to show catheter passing through aorticopulmonary defect into pulmonary artery. For the sake of clarity, the course of the catheter has been traced in.

sound was slightly split and normal in intensity.

The electrocardiogram did not show axis deviation. An angiocardiogram demonstrated a dilated main pulmonary artery. The structures distal to the bifurcation of the artery were poorly opacified, probably indicating a rapid dilution of the dye-containing blood in the main pulmonary artery by arterial blood entering from the aorta.

The results of cardiac catheterization can be seen in Table I. There was a left-to-right shunt into the pulmonary artery which appeared to confirm the diagnosis of patent ductus arteriosus. Mild pulmonic stenosis was also noted.

At the time of surgery in February 1950, no functioning patent ductus arteriosus was found. The ligamentum arteriosum was ligated and divided. A thrill was felt over the main pulmonary artery and conus portion of the right ventricle. The ascending aorta was enlarged to one and a half times its normal diameter. An aortic septal defect was suspected, but not proved. (This case was published at the time.)[10]

Second Admission: The patient was readmitted to the hospital for further evaluation in December 1958, at the age of nineteen; it was felt that surgical correction of the defect was now feasible. Physical examination at this time revealed the blood pressure to be 140/58-40 mm. Hg. The pulse was 80 per minute, regular and collapsing in quality. Systolic and diastolic thrills were associated with a grade 4/4 machinery

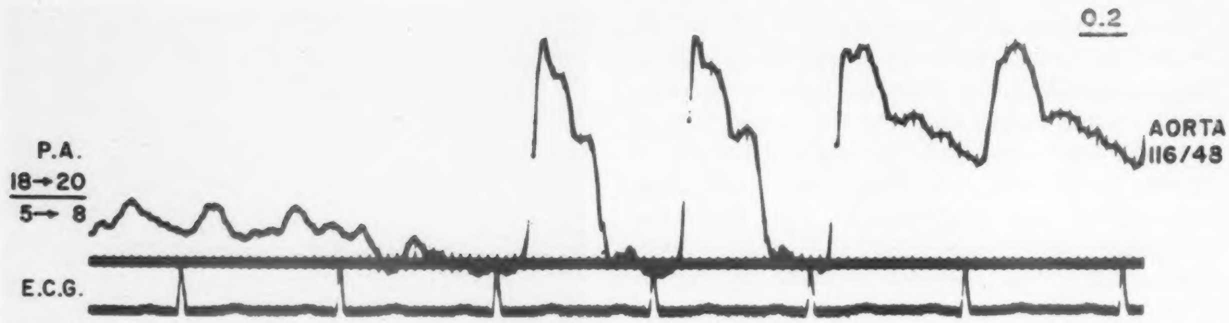

FIG. 2. Pressure recording as catheter tip was pulled back from pulmonary artery to aorta. The nature of the transitional beats is not clear.

murmur in systole and diastole heard loudest in the third intercostal space to the left of the sternum. A localized apical heave was palpated in the sixth intercostal space outside the midclavicular line.

The x-ray film of the chest showed enlargement of the left ventricle and left atrium and prominent pulmonary artery and hilar branches. The electrocardiogram revealed left ventricular hypertrophy. The vectorcardiogram showed a counterclockwise inscribed QRS loop in the horizontal plane. The initial segment of the loop was anterior and to the right; the rest of the loop was posterior and to the left, a pattern seen in biventricular hypertrophy.

A second cardiac catheterization was performed. Initially, a Cournand catheter was introduced through a left antecubital vein and a standard right heart catheterization was performed. A radiopaque Afford catheter was then passed through a No. 16TW needle via percutaneous puncture of the right brachial artery and guided into the mediastinum. After entering the ascending aorta, the catheter curved sharply to the left and slightly downwards (Fig 1). Simultaneous pressures were obtained through this catheter and that in the main pulmonary artery. The mean pressures were identical, although there was considerably more artefact in the pulses obtained through the catheter in the right heart. Moreover, blood samples from both catheters revealed the same oxygen saturation (Table I). A continuous pressure record was taken as the catheter was pulled back from the pulmonary artery to the aorta (Fig. 2).

It was evident that the Afford catheter had traversed an aorticopulmonary septal defect which appeared to have a "take-off" from the aorta at a high level. The catheterization results again demonstrated a left-to-right shunt into the pulmonary artery, and a mild pulmonic stenosis.

Surgery was performed without the need for extracorporeal circulation. Two separate adjacent aorticopulmonary communications were found at the immediate take-off of the aorta and pulmonary artery from the heart. The right coronary artery lay quite close. After careful dissection it was possible to isolate both of the communications. One measured 1 cm. in width, while the other measured 3 cm. The fistulas were divided between clamps and oversewn.

The postoperative recovery was entirely uneventful and the patient was discharged on February 23, 1959.

Summary

Aorticopulmonary septal defect is a rare congenital anomaly which is difficult to diagnose. The prognosis is poor if treatment is not instituted and, therefore, surgery should not be delayed but should be performed as soon as is feasible.

Transection with or without the aid of hypothermia or pump oxygenator is the treatment of choice. A successful case is presented.

References

1. Collett, R. W. and Edwards, J. E. Persistent truncus arteriosus: A classification according to anatomic types. *S. Clin. North America*, 29: 1245, 1949.
2. D'Heer, H. A. H. and van Nieuwenhuizen, C. L. C. Diagnosis of congenital aortic septal defects. *Circulation*, 13: 58, 1956.
3. Bauer, D., deF. and Astbury, E. C. Congenital cardiac disease. *Am. Heart J.*, 27: 688, 1944.
4. Downing, D. F. Congenital aortic septal defect. *Am. Heart J.*, 40: 285, 1950.
5. Gasul, B. M., Fell, E. H. and Casas, R. The diagnosis of aortic septal defects by retrograde aortography. *Circulation*, 4: 251, 1951.
6. Gross, R. E. Surgical closure of an aortic septal defect. *Circulation*, 5: 858, 1952.
7. Scott, H. W., Jr. and Sabiston, D. C., Jr. Surgical treatment for congenital aorticopulmonary fistula. *J. Thoracic Surg.*, 25: 26, 1953.
8. Kirklin, J. W., Ellis, F. H., Jr. and Clagett, O. T. Aortic-pulmonary septal defects. *S. Clin. North America*, 35: 975, 1955.
9. Cooley, D. A., McNamara, D. G. and Latson, J. R. Aorticopulmonary septal defect. *Surgery*, 42: 101, 1957.
10. King, F. H., Gordon, A., Brahms, S., Lasser, R. and Borun, R. Aortic septal defect simulating patent ductus arteriosus. *J. Mt. Sinai Hosp.*, 17: 310, 1951.

Obliterative Brachiocephalic Arteritis (Pulseless Disease)*

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Among the various conditions that give rise to diminished or absent arterial pulsations in the arms, neck and head called collectively "aortic arch syndromes" by Ross and McKusick,[1] there exists a clinicopathologic entity known as obliterative brachiocephalic arteritis, seen mostly in young women. The cause of this disease is obscure. The presence of arterial pulsations in the lower extremities, in contrast to their absence in the upper, led to the designation of "reversed coarctation" by Giffin.[2] Although rare, the disease appears to have a worldwide distribution.[3] Reports of its occurrence in Indians[4,5] are few, and it is therefore considered worthwhile to present this study of a young Indian woman seen in Singapore. An unusual feature of the disease in this patient was the absence of arterial pulsations in all four extremities.

Case Report

An Indian woman aged twenty years was admitted to the General Hospital, Singapore, on August 3, 1956 for segmental resection of a chronic tuberculous lesion in the upper lobe of the right lung. Preoperative examination revealed that radial pulses were absent and she was then referred to the Medical Unit of the hospital for further study. The patient felt well and had no complaints.

Physical Examination: The patient was a slim Indian woman in fairly good nutritional status; secondary sexual characteristics were present. The extremities were warm and well developed. She was afebrile, and did not have cyanosis. There was no clubbing of the fingers or toes.

The radial, ulnar, brachial, axillary, dorsalis pedis, posterior tibial, popliteal and femoral artery pulsations were totally absent and blood pressures were not obtainable in any of the four extremities. Although both carotid arteries were distinctly felt, their pulsations were not forceful; the temporal arteries were palpable without difficulty. Pulsations of the abdominal aorta were felt distinctly. A moderately loud, continuous murmur with systolic accentuation was heard in the left supraclavicular area. A similar murmur, but of lesser intensity, was heard faintly in the suprasternal notch, right supraclavicular area, immediately below both clavicles and at the root of the neck, posteriorly. No thrills were felt in the neck.

Examination of the heart revealed no abnormality. The apex beat was palpable in the fourth left intercostal space 8 cm. from the mid-sternal line and no thrills were felt. The heart sounds were normal and there were no murmurs. No abnormality was found on examination of the lungs, abdomen and central nervous system. The visual acuity was good, there were no cataracts and the fundi were normal.

Laboratory Investigations: Results of blood counts, urinalysis, basal metabolic rate and blood Kahn test were within normal limits. Radiologic examination of the chest showed a normal sized heart and thoracic aorta with normal pulsations. A small fibrotic tuberculous lesion with a small cavity was present in the middle zone of the right lung. Notching of the ribs was not found. The electrocardiogram was normal.

After the patient had been lying still at room temperature (28°C.) for one hour, the mouth temperature was 36.7°C and the skin temperature of her limbs was between 32.1 and 34.3°C. This appeared to be normal, suggesting that the blood flow to the skin of the limbs was adequate at rest and at room temperature. Under these conditions, the oscillations in all her limbs were maximal (30 mm. H_2O) at 60 and 140 mm. Hg. After lying still for fifteen minutes in a room where the temperature was 16°C., her mouth temperature was 36.1°C, and the temperature of her limbs was between 25.9 and 27.5° C. This also was normal as it suggested the existence of vasomotor control in the limbs. Oscillations in her legs and arms were greater after fifteen minutes in the cold room, and a maximum of 50 mm. H_2O was reached at 120 and 220 mm. Hg.

Course: A segmental resection of the affected part of the right upper lobe was carried out.* Post-

* Resection was performed by Mr. H. M. McGladdery.

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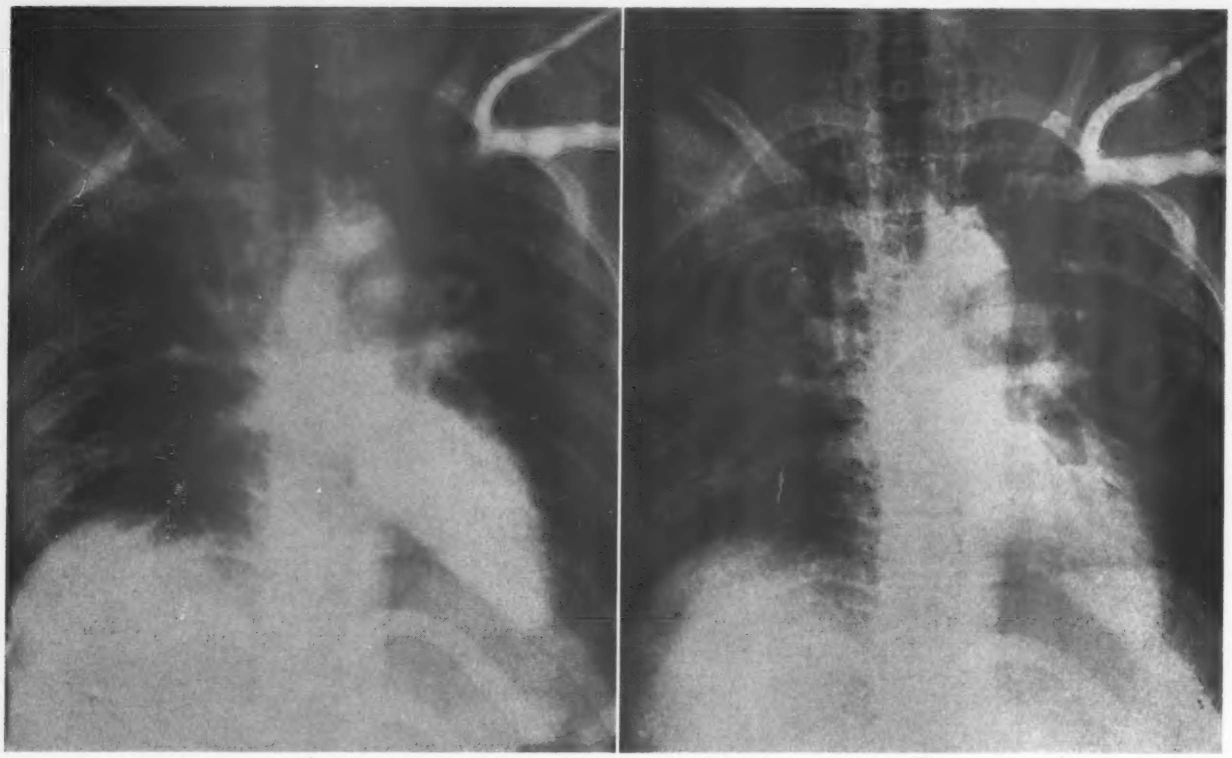

A B

FIG. 1. A, angiocardiogram showing normal aortic arch and thoracic aorta. The left common carotid and subclavian arteries were not visualized while the innominate artery was seen only at its origin from the arch. B, later film showing vertebral arteries and collateral vessels in the neck.

operative convalescence was uneventful. The excised portion of the lung revealed a small fibrotic cavity and histologic examination showed the characteristic features of tuberculosis with cavitation, caseation and fibrosis. The arteries and veins seen in sections of the lung were normal as was a portion of an intercostal artery and vein removed at operation.

She was observed as an outpatient and remained in good health. In April 1958 she was readmitted for further investigations. The physical examination at this time was the same as when she was first seen in 1956. A *biopsy of the right dorsalis pedis artery* was performed. At operation there was no pulsation of the artery, but when it was severed a small trickle of blood flowed out of the cut end of the vessel. Histologic examination of the dorsalis pedis artery and vein showed no significant thickening, occlusion or inflammatory reaction and the muscular and elastic components were within normal limits.

An *angiocardiogram* showed no abnormality of the chambers of the heart. The aortic arch and descending thoracic aorta were well visualized and had a smooth contour without any dilatation or constriction. The left common carotid and left subclavian arteries were not visualized while the innominate artery was visible only at its origin from the arch (Fig. 1A). In later films both vertebral arteries and numerous collateral vessels were clearly seen in the root of the neck (Fig. 1B).

The patient continued to be free of symptoms. On re-examination in September 1958, besides absent pulses in all four extremities, pulsation of the right carotid artery was not felt while the left was palpable, but weak. The abdominal aorta was normally pulsatile.

COMMENTS

In a young woman without arterial pulsations in the upper extremities and in whom there is no evidence of an aneurysm or a congenital anomaly, the diagnosis of obliterative brachiocephalic arteritis is most likely to be correct if the branches of the aorta are not visualized by angiocardiography, as in the patient reported herein. There are, however, several unusual features. This patient had no symptoms referable to her circulatory system. This was probably due to the fact that there was adequate circulation to the head and extremities through collateral vessels. The carotid arteries were palpable. Angiocardiography revealed both vertebral arteries and a network of anastomotic vessels in the neck, and over the extremities normal skin temperatures and oscillometric readings were obtained. In pulseless disease, the frequently reported cerebral and

visual symptoms are considered to be due to impaired blood supply; complaints referable to the arms are only infrequently mentioned.

The tuberculous lesion, which had caused the presenting symptoms, was considered coincidental in view of the high incidence of tuberculosis in Singapore. One patient in the Japanese series had evidence of active pulmonary tuberculosis[6] while a number of them gave positive tuberculin reactions.[7] The significance of the latter finding is difficult to evaluate from an etiologic point of view in countries where tuberculosis is common.

In the descriptions of the disease in the literature, arterial pulses and pressures are recorded as being absent in the upper extremities, but normal in the lower. Rarely, the lower limbs may be affected in association with the upper or alone as shown by the following reports. Ask-Upmark[8] noted absence of pulses and blood pressures in all four extremities in a fifty-eight year old woman who had brachiocephalic ischemia, an arterial murmur in the neck and abnormalities of the eyes. In a forty-two year old woman, who had evidence of inadequate circulation to the head and upper extremities, Gibbons and King[9] suggested involvement of the left iliac artery because the abdominal aorta was normally pulsatile, but the pulsation of the left femoral artery was weak. An interesting report by Correa and Araujo[10] is that of a fifteen year old girl who had palpable arteries and normal pressures in the upper extremities, but none in the lower and was therefore diagnosed as having coarctation of the aorta; death occurred following attempted surgical correction. At necropsy, besides the findings of arteritis of the arch of the aorta and its branches, there was involvement of the descending thoracic aorta which was considerably narrowed with a small lumen, resulting in an impairment of blood supply to the lower extremities; the abdominal aorta and iliac arteries were normal. The angiocardiogram of the patient reported in this paper showed nonfilling of the main branches of the aortic arch; the arch itself and descending thoracic aorta were clearly visualized and not constricted. As the abdominal aorta was normally pulsatile, it is probable that obstruction to blood flow was present at the level of the iliac arteries, thus accounting for the absent pulses in the lower extremities.

The absence of abnormal histologic changes in the small arteries, the intercostal, the dorsalis pedis and those in the resected portion of the lung, are to be noted. However, involvement of visceral arteries[11,12] has been reported and histologic changes in the dorsalis pedis artery have also been found.[11]

Summary

A case of brachiocephalic arteritis in an Indian woman in whom arterial pulsations were absent in all four extremities is reported.

Acknowledgment

We are grateful to Professor E. M. Glaser, Department of Physiology, University of Malaya, for measurement of skin temperatures and oscillometry.

References

1. Ross, R. S. and McKusick, V. A. Aortic arch syndromes. Diminished or absent pulses in arteries arising from arch of aorta. *Arch Int. Med.*, 92: 701, 1953.
2. Giffin, H. M. Reversed coarctation and vasomotor gradient. Report of a cardiovascular anomaly with symptoms of brain tumor. *Proc. Staff Meet. Mayo Clin.*, 14: 561, 1939.
3. Koszewski, B. J. Brachial arteritis or aortic arch arteritis. A new inflammatory arterial disease (pulseless disease). *Angiology*, 9: 180, 1958.
4. Gupta, S. S. N. Pulseless disease. *Bull. Calcutta School Trop. Med.*, 6: 88, 1958.
5. Shah, M. J., Pinto, I. and Patani, S. B. Obliterative brachiocephalic arteritis. *J. Assoc. Physicians India*, 6: 293, 1958.
6. Caccamise, W. C. and Whitman, J. F. Pulseless disease. A preliminary case report. *Am. Heart J.*, 44: 629, 1952.
7. Shimizu, K. and Sano, K. Pulseless disease. *J. Neuropath. & Clin. Neurol.*, 1: 37, 1951.
8. Ask-Upmark, E. On the "pulseless disease" outside of Japan. *Acta med. Scandinav.*, 149: 161, 1954.
9. Gibbons, T. B. and King, R. L. Obliterative brachiocephalic arteritis. Pulseless disease of Takayasu. *Circulation*, 15: 845, 1957.
10. Correa, P. and Araujo, J. Arteritis of the aorta in young women. Report of a case. *Am. J. Clin. Path.*, 29: 560, 1958.
11. Frövig, A. G. and Löken, A. C. The syndrome of obliteration of the arterial branches of the aortic arch due to arteritis. *Acta psychiat. et neurol. scandinav.*, 26: 313, 1951.
12. Ask-Upmark, E. and Fajers, C. M. Further observations on Takayashu's syndrome. *Acta med. scandinav.*, 155: 275, 1956.

Diagnostic Shelf

Ventricular Tachycardia

Importance of Differential Diagnosis in Evaluating Treatment*

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THE clinical studies reported by McGee and Tullis[1] question the classic prohibition against digitalis treatment for ventricular tachycardia. A healthy skepticism about classic injunctions and periodic reappraisal of them will doubtless benefit future patients when the older concepts are fallacious. Contrariwise, hastily discarding them before thorough reconsideration can produce hazards of greater magnitude than potential benefits. The old concepts frequently result from the joint experiences of many investigators and their personal difficulties with the offending agent. Disregard of the classic prohibition may repeat ancient mistakes to the further detriment of other patients. It behooves one to consider alternative diagnostic hypotheses, so that apparent incongruities in observations which result from faulty diagnosis are not attributed to faulty principle.

McGee and Tullis[1] describe the favorable action of digitalis against ventricular tachycardia in two cases but report only one in any detail. In that case (Case 3), the patient experienced a rapid regular tachycardia in the fourth week following a myocardial infarction with consequent signs and symptoms indicating failure of the heart to deliver blood sufficiently rapidly into the greater circulation, a phenomenon not infrequently resulting from tachycardia of diverse origins when the heart has been previously damaged. A strip of electrocardiogram was reproduced in their article (lead I, Figure 1C) showing a regular tachycardia wherein the ventricular depolarization time (QRS) is prolonged to more than 0.12 second. It was interpreted by the authors to reveal "ventricular tachycardia at a rate of approximately 280/minute." Review of the electrocardiographic reproduction with a magnifier fails to reveal clearly any independent atrial rhythm at a rate different from the ventricular. Thus, an alternative explanation that the rhythm could be supraventricular tachycardia with bundle branch block cannot be excluded.

VENTRICULAR VS. ATRIAL TACHYCARDIA WITH BUNDLE BRANCH BLOCK

Esophageal Leads: Recently we have studied a number of patients[2,3] by means of esophageal electrocardiograms as well as by the conventional leads and clinical methods, and have demonstrated otherwise invisible atrial waves. Their number and position proved that supraventricular tachycardia with bundle branch block was frequently and erroneously diagnosed as ventricular tachycardia because the conventional leads alone failed to reveal the real nature of the disturbance. It is really only by demonstrating that an atrial origin is not responsible for the ventricular beats that one can be certain of an idioventricular origin. In some instances, ventricular capture of atrial beats will identify the independent atrial mechanism.

Carotid Sinus Pressure: In other instances, the independence of the atrial and ventricular rates can be proved by slowing the latter, as in

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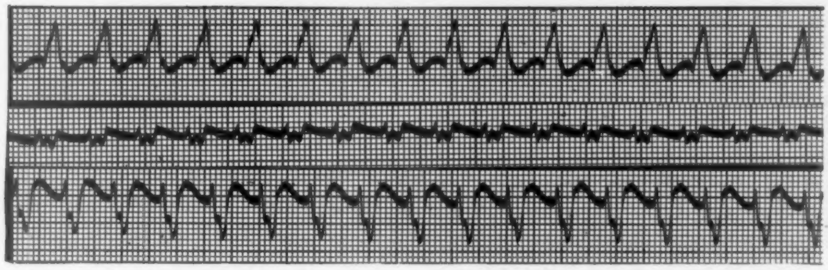


FIG. 1A. Standard leads I, II and III of electrocardiogram during paroxysmal tachycardia, manifested by palpitation, chest pain and dyspnea.

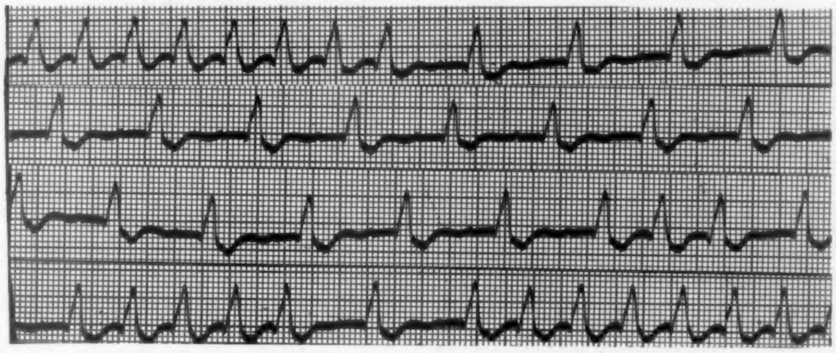


FIG. 1B. Continuous strip of lead I after right carotid sinus massage showing 2:1 atrial tachycardia with bundle branch block.

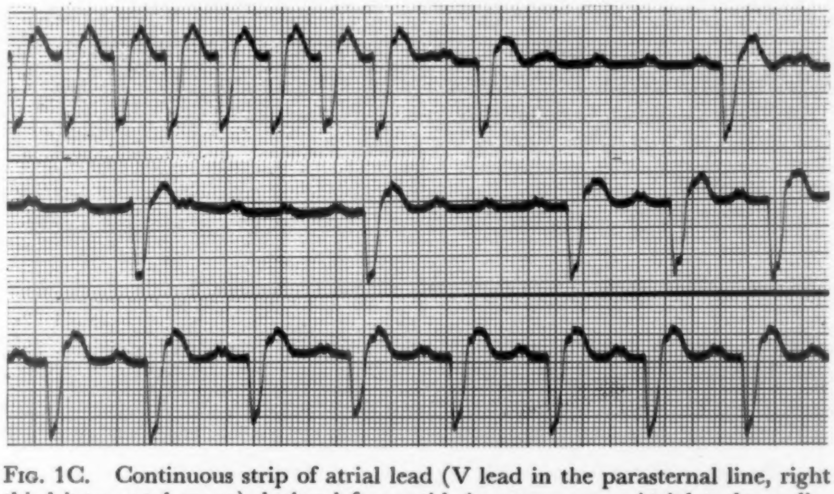


FIG. 1C. Continuous strip of atrial lead (V lead in the parasternal line, right third intercostal space) during left carotid sinus massage. Atrial tachycardia, rate 166 per minute, is evident when ventricular responses are blocked.

Figure 1 (here by carotid sinus massage).

CASE HISTORY

The patient from whom these electrocardiograms were recorded was a forty-seven year old man. He was obese from childhood and preferentially consumed a high fat diet. He weighed 265 pounds at age forty when he experienced his first myocardial infarction. It involved the anterior wall of the heart. Four years later he experienced a second myocardial infarction, this time involving the posterior wall. His terminal illness began in October 1955 with another episode of severe precordial pain lasting three to four hours, followed by development of a persistent intraventricular conduction disturbance in the electrocardiogram. Although the electrocardiographic changes were not diagnostic, they were consistent with further ventricular infarction. Thereafter, he experienced recurring episodes of dyspnea and anginal pain so that by December he was having ten such episodes during the day and seven during the night.

These episodes were precipitated by bouts of atrial tachycardia with intraventricular conduction dis-

turbance (Fig. 1). In this instance pain was typically anginal, produced by the tachycardia and terminated as soon as the tachycardia was controlled. Between episodes, he was free of pain.

He died on January 28, 1956, as the bouts of tachycardia became more prolonged and resistant to therapy. A cerebral hemorrhage occurred terminally. Necropsy confirmed the presence of multiple myocardial infarctions. There was a large aneurysm on the anterior wall of the left ventricle. A large area of recent hemorrhage was present in the brain.

Comments

The similarity of the foregoing to the clinical syndrome reported by McGee and Tullis[1] is noteworthy. Tachycardia occurred in the postinfarction period, albeit after the patient's third episode of myocardial infarction. It differs in location of intraventricular block, involving the left branch of the bundle of His; whereas, in the case reported by McGee and Tullis, it would have involved the right branch if representing the mechanism alternatively hypothesized (supraventricular tachycardia with bundle branch block). It is regrettable that absolute evidence is wanting in their case to distinguish between a ventricular and supraventricular origin of the tachycardia. The frequent salutary effect of digitalis in the latter may make it the more likely explanation; but, since there are no independent criteria, one cannot exclude the possibility that digitalis did have a favorable effect in an instance of ventricular tachycardia.

We must seek indisputable evidence of ventricular tachycardia in patients to be seen in the future wherein all other measures appear to be fruitless and for whom the risk of digitalis therapy appears to be warranted by the desperate clinical situation. From the report of such cases, we should ultimately be able to ascertain whether or not the trial of digitalis is justifiable but, in the meantime, the cardiologist should be loathe to break the classic injunction[4,5] against the use of digitalis in ventricular tachycardia.

References

1. McGee, R. R. and Tullis, I. F. Ventricular tachycardia, with particular consideration of digitalis therapy. *Am. J. Cardiol.*, 3: 300–306, 1959.
2. Wehrmacher, W. H. and Anderson, D. A. Esophageal electrocardiography: a reclaimed diagnostic method. *Circulation*, 18: 796, 1958.
3. Wehrmacher, W. H. and Anderson, D. A. Third World Congress of Cardiology, Brussels, 1958. Abstracts of communications, p. 368–369.
4. Massey, F. C. Clinical Cardiology, p. 869. Baltimore, 1953. Williams & Wilkins Co.
5. Lown, B. and Levine, S. A. Current Concepts in Digitalis Therapy, p. 105. Boston, 1954. Little Brown and Co.

Progress Notes in Cardiology

Edited by Emanuel Goldberger, M.D., F.A.C.C.
New York, New York

Are Coronary Disease Mortality Data Valid?

Mark Twain once said, "There are three kinds of lies—plain lies, damn lies, and statistics." A fascinating and valuable recent report by Dr. Lewis D. Williams (*Pennsylvania M. J.*, 62: 1113, 1959) on the mortality data of coronary artery disease, based on death certificates, seems to bear this out. He studied a total of 3,557 death certificates, with particular attention to those in which the cause of death was listed as: coronary occlusion, coronary thrombosis, coronary disease, coronary infarction, coronary embolism, coronary heart disease or myocardial infarction or infarct. He then challenged the accuracy of these certificates, based on the following three criteria:

(1) The deceased was not attended by the attesting physician at some time previous to the last two hours of life, or was not attended at all during the stated period of coronary illness and no autopsy was performed.

(2) The certificate was not signed by a physician, and no autopsy was performed. (The signer was a non-medical person.)

(3) The certificate contained no data regarding duration of illness, period of physician's attendance or time of death and no autopsy was performed.

Of the 3,557 deaths reported, 911 were certified as due to coronary artery disease. On this basis, the incidence of death due to coronary artery disease was 1 in 3.9. However, after screening the death certificates by means of the above criteria, Dr. Williams found that the incidence of coronary deaths was 1 in 7.2. In other words, the incidence of coronary artery disease based on death certificates is apparently 50 per cent too high.

If this study can be corroborated, it means that coronary artery disease is not the killer that we have been led to believe.

The Shock Syndrome Associated with Bacteremia due to Gram-Negative Bacilli

Drs. Max H. Weil and Wesley W. Spink (Department of Medicine, University of Minnesota Medical School, Minneapolis) made a study of the clinical features of 400 patients who were hospitalized at the University of Minnesota Hospitals in the period between January 1950, and September 1955 with bacteremia due to gram-negative enteric bacteria. There was no reasonable doubt that bacteremia existed in 278 of these patients. It was complicated by hypotension and signs of shock in forty-three of these patients.

In more than 90 per cent of the patients with shock, a procedure performed in the hospital was implicated. This included instrumentation of the lower urinary passages, septic complications of surgery, cannulation of a peripheral vein, administration of intravenous fluids under unfavorable conditions of sterility and paracentesis. Signs of sepsis, including chills and fever, followed within forty-eight hours of the causative event, and shock appeared approximately twelve hours later. Nausea, vomiting and diarrhea usually accompanied the onset of shock. The leukocyte count and percentage of neutrophils were notably increased. A majority of patients had significant electrocardiographic abnormalities, which made differentiation from shock caused by myocardial infarction very difficult in many instances. It is important to obtain a blood culture in instances where the cause of shock is not apparent. This is of value not only for the establishment of a specific diagnosis but also for planning optimal antibiotic therapy.

The mortality rate of patients with bacteremia and shock was 65 per cent, with death occurring at an average of 2.7 days after onset of shock.

The mean duration of the state of shock for patients who survived was six days (twelve hours to twenty-six days), indicating the protracted course of this type of shock. Acute renal failure may become an important factor during the recovery period and was the cause of death in four patients of the present series.

Readings in Cardiology

Evaluation of New Procedures and Drugs: The development of a new drug or a new treatment often follows a characteristic course. First, the overenthusiasm of the innovator is met with indifference or outright rejection. This may be followed by grudging acceptance of the new technic, still later by overenthusiastic acceptance and finally by a more sober recognition of the value of the new treatment. This may lead to an unwarranted rejection.

The reaction of the medical profession to the value of bilateral internal mammary artery ligation in the treatment of angina pectoris has followed much the same course. The overenthusiasm for the operation was suddenly brought to a halt when it was shown that a sham operation could produce the same percentage of cures. In addition, physiologic evidence that the operation causes an increased coronary artery blood flow is dubious.

The discrepancy between the early and late results of this procedure is due partly to the fact that the physician, turned scientist, is not familiar with the basic principles of scientific research. Two recent books* describe methods of avoiding such pitfalls.

Ingle's stimulating book discusses a wide range of subjects, such as the effect of suggestion, mental attitudes, causality, probability, chance, methods of avoiding errors in sampling, personal errors, fallacies, principles of testing, experimental design and interpretation of results.

In Waife and Shapiro's book, fourteen authorities present a survey of the many problems involved in the evaluation of new drugs, from the initial pharmacologic and toxicologic studies in animals, through clinical trials. Here again, it is forcefully shown that many of the clinical reports of new drugs which appear in the medical literature are testimonials rather than objective scientific evaluations.

These two books are required reading not only for the medical investigator but for the practicing physician as well.

Sickle Cell Anemia: The patient with sickle cell anemia often presents signs of cardiac enlargement or of cor pulmonale. The cardiac enlargement is due to the fact that during a sickle cell crisis, severe anemia develops. This can cause hemic murmurs and cardiac enlargement. In addition, small multiple thromboses occur in blood vessels throughout the body, including the lungs. This increases the pulmonary resistance and cor pulmonale later develops. Thromboses of small blood vessels near joints can also produce an arthritic type of pain, which resembles the arthritis of rheumatic fever.

From a clinical point of view sickle cell anemia should be differentiated from the sickle cell trait. The reason for this difference was obscure until 1949 when Pauling and his coworkers made the fundamental discovery that the red blood cells of the patient with sickle cell anemia contain an abnormal hemoglobin S, whose molecular structure is slightly different from the normal hemoglobin A. The patient with sickle cell anemia has hemoglobin S derived from both parents. The patient with the benign sickle cell trait has normal hemoglobin A derived from one parent, in addition to hemoglobin S.

The genetic as well as the clinical problems of this disorder have been excellently summarized in a new book by Hsia.† He not only discusses sickle cell anemia and other disturbances of hemoglobin synthesis, but also other inborn errors of metabolism associated with cardiovascular disease, such as diabetes, glycogen storage disease, cretinism, adrenogenital hyperplasia associated with hypertension and primary hypercholesterolemia, as well as numerous other hereditary disturbances whose significance we are just beginning to appreciate.

*** Principles of Research in Biology and Medicine, by Dwight J. Ingle. J. B. Lippincott Co., Philadelphia, 1958.**

A Clinical Evaluation of New Drugs by 14 Authors, edited by S. O. Waife and Alvin P. Shapiro. Paul B. Hoeber, Inc., New York, 1959.

† Inborn Errors of Metabolism, by David Yi-Yung Hsia. The Year Book Publishers, Inc., Chicago, 1959.

Cardiac Resuscitation

Edited by Paluel J. Flagg, M.D., F.A.C.C.*

New York, New York

The Treatment of Cardiac Asystole

Robert M. Hosler, M.D.

Cleveland, Ohio

The heart may suddenly cease to function with resultant arrest of the circulation. In the operating room and recovery room, two distinct conditions of arrest are encountered, cardiac asystole or standstill and ventricular fibrillation. Due to its particular pattern of excitability, human cardiac muscle will not undergo cardiac stoppage in a state of systole, as does the turtle heart. Although there are many variables which influence the type of arrest, in general it can be said that cardiac asystole will occur in about 80 per cent of these catastrophes.

In the state of cardiac asystole the heart is motionless. In the event of its rapid exposure it can be observed that this ordinarily dynamic organ is somewhat dilated and cyanotic. Upon rare occasions it may be found to undergo a few slow ineffectual beats. In this situation, nevertheless, there is no pumping action of the heart. This particular finding commonly indicates that resuscitation can be accomplished as the heart has not yet lost its excitability, one of its inherent properties. Oxygen-depleted cardiac muscle will completely lose its excitability in a matter of thirty to sixty seconds. Our laboratory work[1] would indicate that the dividing line is nearer forty-five to fifty seconds.

This significant fact is of importance in considering the restoration of the heart beat by physical stimulation, such as pounding on the chest, the application of a pacemaker stimulus or the employment of an external defibrillating shock.[1] In order to return the myocardium to a state of excitability after one minute of cessation or circulation, the oxygen tension must be increased in the capillaries so that it will be available to the cells. It becomes apparent that a means of providing oxygen to the coronary system is imperative. There are two practical means for the accomplishment of this: (1) manual cardiac massage and (2) intra-arterial transfusion under pressure. These will be discussed later.

The cardiac resuscitation procedure must be separated into two distinct steps according to Beck. They are: (1) re-establishment of the oxygen system and (2) restoration of the heart beat. The importance of each simple step in its proper sequence cannot be overemphasized.

Step I. Re-establishment of the Oxygen System

It is important to know the things to do and the things not to do during those critical moments when a life is hanging in the balance. Too often, temporizing time-consuming measures are carried out. In the meantime the oxygen deficiency of the upper centers of the brain has resulted in permanent damage to that vital organ.

A definite step by step plan must be put into effect at once. The surgeon must be so geared to this that in the existing confusion he can perform the proper steps reflexly. Most failures are attributed to the so-called time limitation. This time limitation of three to four minutes must be overcome: otherwise the victim's

* President, National Resuscitation Society, Inc., 2 East 63rd Street, New York 21, New York.

brain is irreversibly damaged, although the heart beat and circulation have returned to normal.

It is obvious that not a second should be wasted. The moment that the anesthetist can adequately aerate the lungs (intratracheal intubation and 100 per cent oxygen are preferred), the surgeon proceeds to incise the left chest. The surgeon estimates the fourth or fifth interspace and makes a deliberate and large intercostal incision. This should extend from the edge of the sternum to the underlying sheet. Later, the internal mammary artery may have to be secured; this is to be hoped for.

The right hand is now thrust into the chest cavity, pushing the lung posteriorly; then the hand is guided behind the heart and its intact pericardium. The heart with its pericardium is compressed against the sternum and thus massage is begun.[2] The crisis is now over, the oxygen system is re-established. The patient is protected. Time can be taken to restore the heart beat.

By this time the operator's wrist may be virtually strangulated between the ribs, especially if the anesthetist is ventilating the lungs properly. A short pause is taken to cut the costochondral junctions of the two adjacent ribs, thus permitting more room. Additional manual emptying of the heart is undertaken immediately. A short time later a large self-retaining retractor is introduced, and the pericardium opened from the base to the apex. Quickly the bare heart is grasped in the hand and massage again instituted. A circulation adequate to maintain life for hours can be sustained. A more effective circulation can be developed by squeezing the bare heart. However, on exceptional occasions the heart beat and circulation will be restored before the pericardium need necessarily be opened.

STEP 2. RESTORATION OF THE HEART BEAT

If this procedure has been carried out with dispatch, up to this juncture it is not known whether the heart is in standstill or fibrillation. Since the restoration of the heart beat is somewhat different in the two conditions, the surgeon now stops momentarily and observes the ventricles. If there are no fibrillary movements, he can assume that the heart is in a state of asystole or standstill.

If the heart should not resume its rhythmic beat after effectual massage and good ventilation have been carried out for several minutes, 3 to 5 cc. of 1:10,000 epinephrine solution are injected into the chamber of the right ventricle and massage continued. This solution should be injected into the lumen or chamber and not into the myocardium.

In many instances the heart will begin to beat if all conditions are favorable. If it fails to do so the surgeon should check the excursion of the lungs and observe the color of the myocardium. The latter is a very valuable sign as it indicates the effectiveness of the restoration of the oxygen system. Good oxygenation of the lungs and adequate blood flow to the myocardium are essential in any attempt to revive the heart.

Assuming that after three to five minutes of adequate massage there is still no spontaneous heart action, epinephrine can be injected for a second and third time and warm saline[2] can be poured on the surface of the heart. If the heart is not in ventricular fibrillation and if it fails to produce rhythmic beats, the reason may be faulty aeration of the lungs, faulty massage technic, peripheral circulatory failure, massive pulmonary embolism, inadequate elimination of carbon dioxide or intrinsic cardiac disease. After repeated injections of epinephrine it might be efficacious to substitute calcium gluconate; nevertheless epinephrine solution remains the cardiac stimulant par excellence.

Once a rhythmic beat is obtained, it is recommended that $\frac{1}{150}$ gr. of atropine sulphate be given intravenously, followed by 4 cc. of lanatoside C. Improvement of the coronary and cerebral circulation can be carried out on a temporary basis by pinching the thoracic aorta with the thumb and finger, thus directing more blood into those vessels at the root and arch of the aorta. The aorta should not be shut off for longer periods than one-half minute at various intervals.

The chest is closed only when it is determined that the circulation is satisfactory. It is a wise plan to observe the action of the heart for some time; much can be learned from visual observation. The heart can undergo stoppage again as well as occasionally "slip into" ventricular fibrillation. A great deal of diligent and intelligent postresuscitative care must be started in the operating room. The patient should not be taken back to his room immediately. Ice bags may be placed around the patient, and blood or glucose may be

judiciously administered as well as a vasopressor if indicated.

Adequate aeration of the open chest followed by massage of the exposed heart remains the best of present day methods for cardiac resuscitation. All persons who suddenly undergo clinical death cannot be reanimated; however, an institution over a period of time should not passively accept a record of less than 50 per cent successful resuscitations.

Intra-Arterial Transfusions

Some[1,3,4] have experienced good results in restoring the heart beat by directing oxygenated blood into the coronary system by employing intra-arterial transfusions under pressure with the stream directed toward the arch of the aorta. Usually an artery such as the brachial or lower posterior tibial has been previously surgically exposed. This procedure obviates the unpleasant and forbidding task of opening the chest, but in many hands this procedure can be just as formidable and more time-consuming. It does fulfill the requirement of delivering oxygenated blood into the coronary system under a minimum pressure of at least 40 mm. Hg.[5] At times hydrogen peroxide has been added to the intra-arterial transfusion.[6]

Electrical Pacemaker

The stimulus to initiate a heart beat supplied by a pacemaker is usually successful if applied during a period of little more than thirty seconds after cardiac arrest, in other words, following complete cessation of the coronary circulation. This leaves little time if previous planning and arrangements have not first been carried out and their use specifically anticipated. As stated before, to be successful a physical stimulus alone must be applied or delivered before the period of excitation of the anoxic cardiac muscle cells has been terminated. The pacemaker therefore, does not have much opportunity for success in the ordinary case of cardiac arrest that suddenly confronts the surgeon. It has found its proper niche in the treatment of heart block from surgical damage to the conduction system and especially in the Stokes-Adams syndrome and in certain phases of hypothermia.

An understanding of the pattern of excitability of the mammalian cardiac muscle would indicate that repeated pounding on the chest of an unfortunate person with cardiac stoppage is futile. It would seem permissible to try it once, if one suspects that cessation of the circulation has just occurred. Observation of such hearts in the laboratory indicates that a progressing cyanosis is quickly visible. It is now accepted that a physical stimulus applied to a cyanotic heart is seldom, if ever, successful in restoring a rhythmic heart beat and, most important of all, an adequate circulation.

Resuscitation is still in its infancy; nevertheless, prevention is the best treatment. Planning for such an eventuality is one of the best ways to avert it. This planning must be on an individual as well as an institutional basis, if better results are to be obtained. Preparation and education will save lives and time-consuming indecisions.

References

1. (*a*) Hosler, R. M. and Wolfe, K. Open chest versus closed chest resuscitation. *Am. J. Surg.*, 97: 739, 1959.
   (*b*) Hosler, R. M. and Wolfe, K. Closed chest resuscitation. *Arch. Surg.*, 79: 31, 1959.
2. Hosler, R. M. A Manual on Cardiac Resuscitation, 2nd ed. Springfield, Ill., 1958. Charles C Thomas.
3. Crile, G. W. Anemia and Resuscitation. New York, 1914. D. Appleton & Co.
4. Negovski, V. A. et al. Experiment on the treatment of terminal states. *Surgery* (*Moscow*), 9: 11, 1952.
5. Sollman, T. Revival of excised mammalian heart. *Am. J. Physiol.*, 15: 121, 1905.
6. Shikanova, L. G. Use of oxygenated blood in the restoration of vital functions. Presented at the Academy of Medical Sciences, Moscow.

* * *

The American Academy of General Practice has authorized as acceptable for category I, credit 10 hours, the Resuscitation Course given by the National Resuscitation Society. This authorization covers the courses to be given on February 4, 5, April 7, 8 and June 2, 3, 1960. Notification was received from Dr. A. Pincus, Director of Postgraduate Education of the Academy.

The Query Corner

READERS are invited to submit queries on all aspects of cardiovascular diseases. Insofar as possible these will be answered in this column by competent authorities. The replies will not necessarily represent the opinions of the American College of Cardiology, the JOURNAL or any medical organization or group, unless stated. Anonymous communications and queries on postcards will not be answered. Every letter must contain the writer's name and address, but these will not be published.

Cardiovascular Complications Following Electroshock Therapy

Query: Please discuss some of the clinical problems involved in evaluating and treating the patient with heart disease who requires electrical shock therapy.

Answer: These observations summarize our experiences with fatal cardiovascular accidents observed to have followed approximately 100,000 electroconvulsive treatments to 17,000 patients over a period of twelve years at the West Hill Sanitarium.

The more recent use of atropine to avoid extravagal factors and the intravenous use of barbiturates and succinylcholine (Anectine®) chloride intravenously as well as ventilation with 100 per cent oxygen during the apneic phases of treatment, have in no way prevented fatal cardiovascular accidents. It has been found impossible to avoid such fatalities with the best means at our disposal.

Angina Pectoris: One woman with angina pectoris died immediately following treatment. Infarction of the heart developed in six patients.

Infarction of the Heart: There were fourteen deaths that could be attributed to this condition. In nine, death occurred immediately after treatment and in five, within the first twenty-four hours after therapy. The ages of the patients ranged between forty-two and sixty-four years. None had any symptoms except electrocardiographic changes of healed infarcts of at least four months' duration. Confirmation at autopsy revealed healed infarcts in five and fresh thrombi of the coronary arteries in two.

Atrial Fibrillation: Two women with mitral stenosis, both under thirty years and one woman aged sixty years with arteriosclerotic heart disease died after treatment in the course of atrial fibrillation with well controlled ventricular rates in the absence of congestive heart failure.

Subacute Bacterial Endocarditis: In a young woman with an unsuspected streptoccocus viridans infection of the mitral valve, numerous emboli to the brain developed following treatment and she died as a result of these.

Thrombosis of the Carotid Artery: In a fifty-four year old woman, coma developed immediately after treatment. Operative intervention on the brain revealed the presence of a fresh thrombus involving the whole of the right carotid artery.

Persistent Convulsions: In one patient with antecedent cerebrovascular accidents and in another with diffuse disease of the arteries of the brain, electroshock therapy resulted in persistent convulsions lasting twenty-four and sixty-two hours, respectively, and ending in death.

Conclusions: The intimate factors responsible for precipitating death in these patients are still unknown. It would be best to avoid electroshock therapy in patients with angina pectoris, recent infarction of the heart, subacute bacterial endocarditis or in those in whom cerebrovascular accidents would be liable to yield convulsions.

SIDNEY P. SCHWARTZ, M.D.
BERNARD PACELLA, M.D.
New York, New York

College News

1960 Workshop Program

This year's program is limited to a selected schedule of six important workshops which are believed to be particularly attractive to members of the College.

The Workshop Program is not only edifying and valuable but represents the realization of one of the College's most fundamental raisons d'etre.

Members of the College are urged to take advantage of this opportunity offered by your Postgraduate Education Committee by communicating with Dr. Philip Reichert, Executive Secretary, 350 Fifth Ave., New York 1, New York, relative to arrangements for participation. Due to the limited number of students for each workshop, early registration is advised.

Clinical Workshop Program 1960

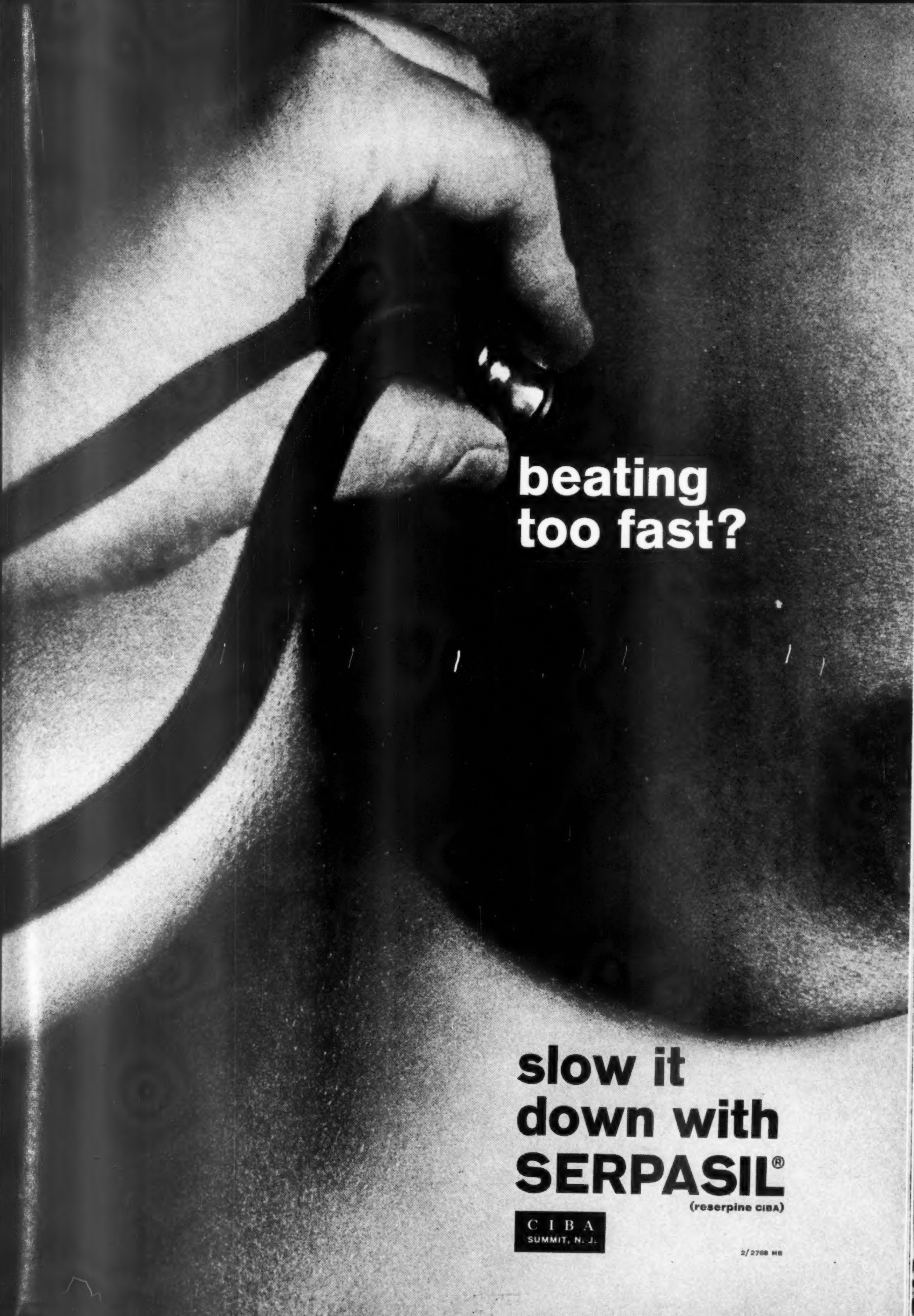
Date (1960)	Preceptor	Subject	Place	Maximum No. of Students
February 9, 10, 11	Dr. Ignacio Chavez	Broad aspects of meeting cardiologic problems; diagnosis and treatment	National Heart Institute, Mexico, D. F., Mexico	10
March 31	Dr. Emanuel Goldberger	How to determine if a cardiac patient (congenital or acquired) will benefit from cardiac surgery	Montefiore Hospital 210th St. and Bainbridge Ave. New York, N. Y.	50
April 10–16	Dr. Robert P. Glover	Intimate contact with problems of diagnosis and treatment of patients suitable for cardiac surgery (possibility of scrubbing with Dr. Glover)	The Glover Clinic 269 S. 19th St. Philadelphia 3, Pa.	3
May 16–22	Dr. Benjamin Gasul	What we must know about congenital heart disease; diagnosis and management	Cook County Children's Hospital 700 South Wood Street Chicago, Ill.	8
June 6–11	Dr. Oscar Magidson	Indications and contraindications to open heart surgery; practical considerations	St. Vincent's Hospital 2131 W. 3rd St. Los Angeles 57, Calif.	8
June 9, 10	Dr. Ashton Graybiel	Stress and the cardiovascular system in space medicine	U. S. Naval Aviation Medical Center Pensacola, Fla.	5

Workshop at Montefiore Hospital, Rosenthal Auditorium

March 31, 1960, 10:00 A.M.–5:00 P.M.

How to Determine if a Patient with Acquired or Congenital Cardiac Lesions will Benefit from Cardiac Surgery

10:00 A.M.–10:10 A.M.	**Welcoming Address,** E. GOLDBERGER, M.D.
10:10 A.M.–10:45 A.M.	**X-ray Configurations in Acquired Heart Disease.** H. JACOBSON, M.D., J. SHAPIRO, M.D., B. RUBENSTEIN, M.D., C. ENSELBERG, M.D. Case presentations showing the criteria for chamber enlargement (MS, MI, AS, AI, TI).
10:45 A.M.–11:45 A.M.	**Cardiac Catheterization and Phonocardiography.** D. ESCHER, M.D., R. EISENBERG, M.D., R. ROSENBLUM, M.D., A. BUCHBERG, M.D., B. JACOBSON, M.D. Cases showing use of gas and dye analysis, pressure curves, etc., and phonocardiography.
11:45 A.M.–12:30 P.M.	**X-ray Configurations in Congenital Heart Disease.** B. SCHWEDEL, M.D., H. JACOBSON, M.D., W. STERN, M.D., R. EISENBERG, M.D. Cases showing characteristic angiocardiographic configurations.
12:45 P.M.– 1:15 P.M.	**Lunch**
1:15 P.M.– 1:30 P.M.	**Welcoming Address,** L. LEITER, M.D.
1:30 P.M.– 2:40 P.M.	**Electrocardiography.** E. GOLDBERGER, M.D., S. P. SCHWARTZ, M.D., I. RUBIN, M.D., H. MARK, M.D. Cases showing typical and atypical patterns in acquired and congenital lesions.
2:40 P.M.– 3:50 P.M.	**Surgery in Acquired Heart Disease.** A. JEZER, M.D., E. HURWITT, M.D., H. GROSS, M.D., B. BURACK, M.D. Discussion of criteria for surgery, results of operations, the problem of restenosis, myocardial factors, vs. mechanical valvular factors, arrhythmias developing during surgery, postvalvulotomy therapy.
4:00 P.M.– 5:00 P.M.	**Surgery for Congenital Heart Disease.** D. YOUNG, M.D., G. ROBINSON, M.D., D. ESCHER, M.D., J. FRIEDEN, M.D. Discussion of bypass vs. hypothermia, criteria for operation, results, future outlook. (IASD, IVSD, PD, tetralogy, P.S. a-v communis, coarctation.)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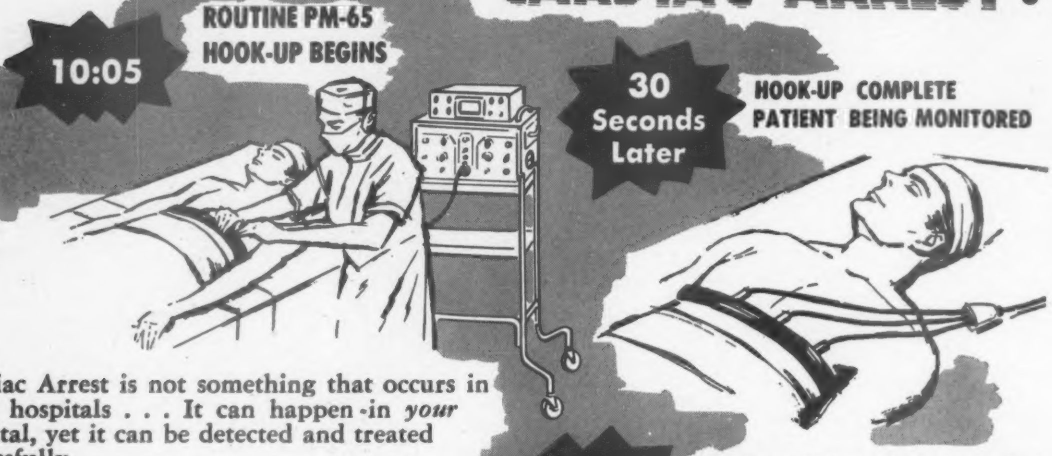

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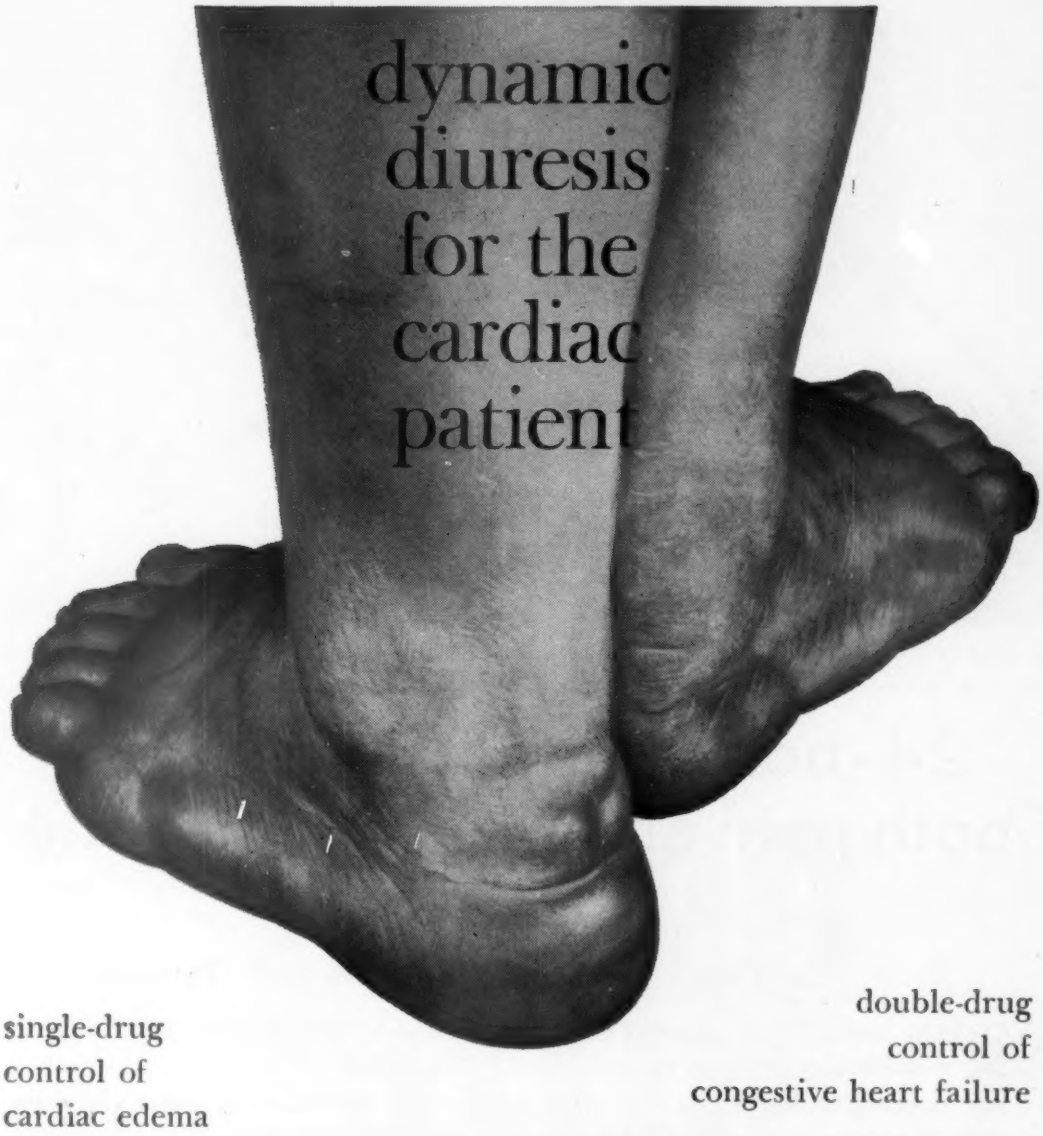

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1. Feinblatt, T. M., and Ferguson, E. A.: New Eng. J. Med. 256:331 (Feb.) 1957.
2. Kupersmith, I. H.: International Record of Medicine, Vol. 171 No. 10 (Oct.) 1958.
3. Berry, J. W., and Roach, T. C.: Circulation, Vol. 17, No. 6 (June) 1958.

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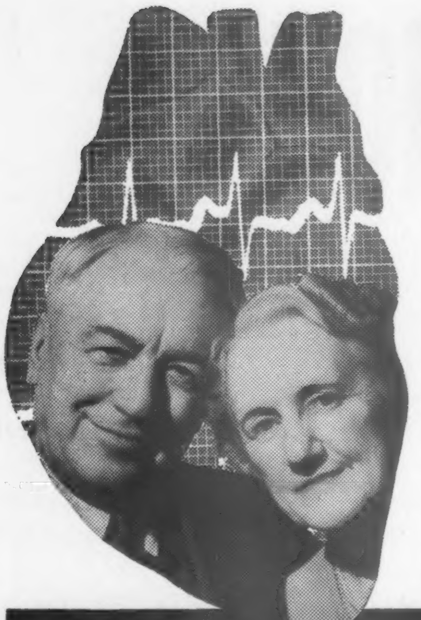

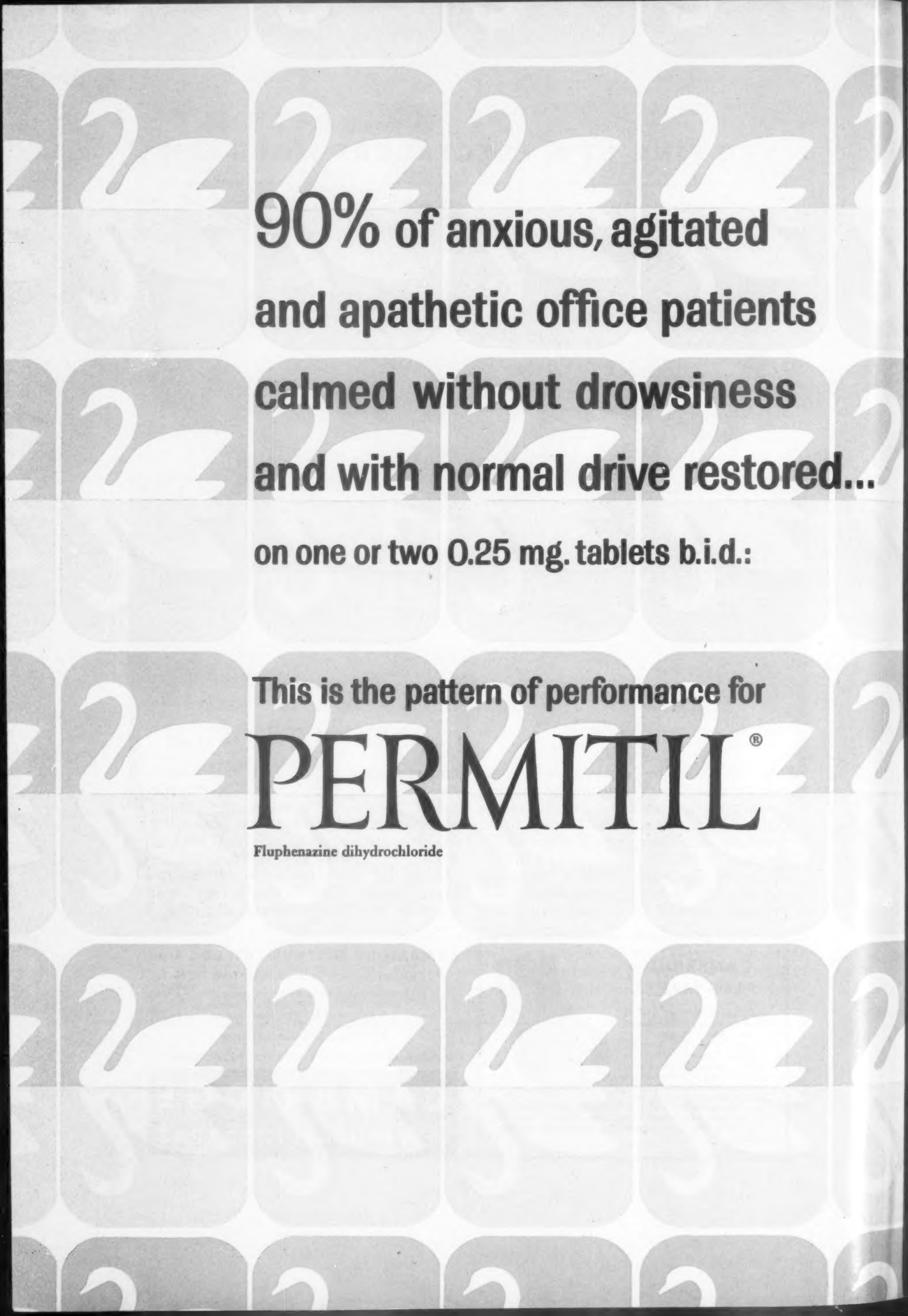
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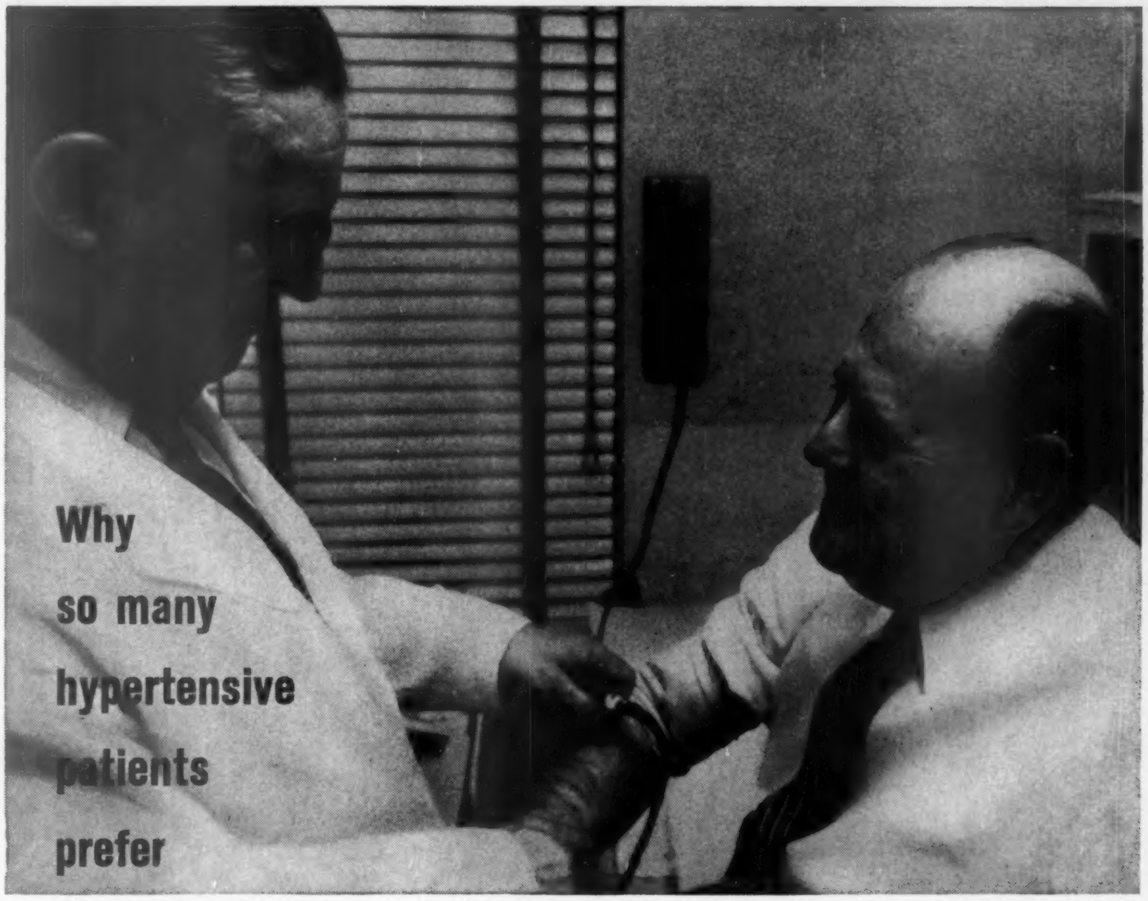

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*Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. 169:1609 (April 4) 1959.

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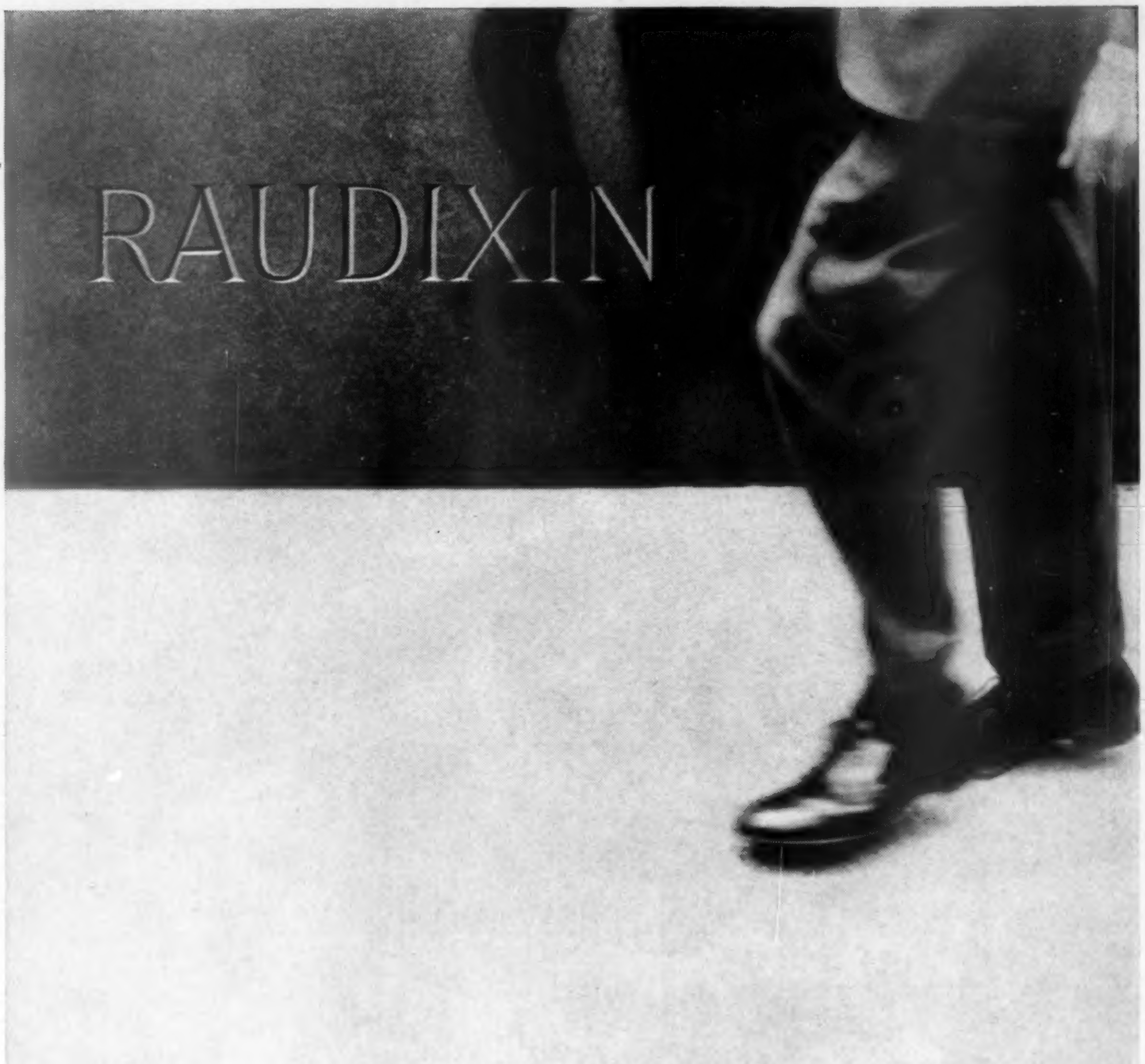
(1) Mayer, G. A., and Connell, W. F.: Canad. M.A.J. 77:930 (Nov. 15) 1957.
(2) Burke, G. E., and Wright, I. S.: Circulation 3:164, 1951.
(3) Vander Veer, J. B., Funk, E. H., Jr., Boyar, F. R., and Keller, E. A.: Am. J. Med. 14:694, 1953.
(4) Scarrone, L. A., Beck, D. F., and Wright, I. S.: Circulation 6:489, 1952.
(5) Neill, E. C.; Moon, R. Y., and Vander Veer, J. B.: Circulation 15:213, 1957.
(6) Rullo, F. R.; Bartels, C. C., and Evans, J. A.: J.A.M.A. 168:743 (Oct. 11) 1958.
(7) Menendez, C.; Almonte, J. C., and Ramos, C. N.: Angiology 8:182, 1957.
(8) Mayer, G. A., and Connell, W. F.: Canad. M.A.J. 76:272 (Feb. 15) 1957.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